Dose-response Data and BMD Curves from EPL (2011) and Dodd *et al*. (2012)

Lesion Code and Description

Lesion Code	Lesion Location	Lesion Description
m_rea	Ventral Respiratory	male rat nasal respiratory epithelial adenoma
f_rea	Ventral Respiratory	female rat nasal respiratory epithelial adenoma
m_oen	Dorsal Olfactory	male rat nasal olfactory epithelial neuroblastoma
f_oen	Dorsal Olfactory	female rat nasal olfactory epithelial neuroblastoma
m_reh	Ventral Respiratory	male rat respiratory epithelium - hyperplasia (2 year study)
m_resm	Ventral Respiratory	male rat respiratory epithelium - squamous metaplasia (2 year study)
m_oed	Dorsal Olfactory	male rat olfactory epithelium - Degeneration (2 year study)
m_oeh	Dorsal Olfactory	male rat olfactory epithelium - hyperplasia (2 year study)
f_reh	Ventral Respiratory	female rat respiratory epithelium - hyperplasia (2 year study)
f_resm	Ventral Respiratory	female rat respiratory epithelium - squamous metaplasia (2 year study)
f_oed	Dorsal Olfactory	female rat olfactory epithelium - Degeneration (2 year study)
f_oeh	Dorsal Olfactory	female rat olfactory epithelium - hyperplasia (2 year study)
m_oeic	Dorsal Olfactory	male rat olfactory epithelium - inflamation chronic (2 year study)
f_oeic	Dorsal Olfactory	female rat olfactory epithelium - inflamation chronic (2 year study)
m_gch	Ventral Respiratory	male rat respiratory epithelium – goblet cell hyperplasia (2 year study)
m_gch_9	Ventral Respiratory	male rat nasopharyngeal duct - goblet cell hypertrophy/hyperplasia (90 day study)
f_gch	Ventral Respiratory	female rat respiratory epithelium – goblet cell hyperplasia (2 year study)
f_gch_9	Ventral Respiratory	female rat nasopharyngeal duct - goblet cell hypertrophy/hyperplasia (90 day study)
m_reh_9	Ventral Respiratory	male rat respiratory epithelium - hyperplasia (90 day study)
m_resm_9	Ventral Respiratory	male rat respiratory epithelium - squamous metaplasia (90 day study)
m_oed_9	Dorsal Olfactory	male rat olfactory epithelium - Degeneration (90 day study)
m_oeh_9	Dorsal Olfactory	male rat olfactory epithelium - hyperplasia (90 day study)
f_reh_9	Ventral Respiratory	female rat respiratory epithelium - hyperplasia (90 day study)
f_resm_9	Ventral Respiratory	female rat respiratory epithelium - squamous metaplasia (90 day study)
f_oed_9	Dorsal Olfactory	female rat olfactory epithelium - Degeneration (90 day study)
f_oeh_9	Dorsal Olfactory	female rat olfactory epithelium - hyperplasia (90 day study)
m_nt_inflam	Dorsal Olfactory	male rat nasal tip epithelium inflammation (90 day study)
f_nt_inflam	Dorsal Olfactory	female rat nasal tip epithelium inflammation (90 day study)**
m_nt_inflam_rec	Dorsal Olfactory	male rat nasal tip epithelium inflammation, 4 weeks post recovery (90 day study)
f_nt_inflam_rec	Dorsal Olfactory	female rat nasal tip epithelium inflammation, 4 weeks post recovery (90 day study)**

Quantitative Consideration of the Severity of Lesions Using Quantal BMDS Modeling Techniques

Female REH Lesions in the Subchronic (90-Day) Dodd et al. (2012) Study

Group	1	2	3	4	5
Amt Mtb (nmol/min-g)	**0**	**0.912448**	**4.438954**	**7.122926**	**7.547781**
Number Examined	10	10	10	10	10
With f_reh lesion*	0	0	10	9	9
Severity 1	0	0	10	2	3
Severity 2	0	0	0	7	6
Severity 3	0	0	0	0	0
Severity 4	0	0	0	0	0
Severity 5	0	0	0	0	0
Average Severity	--	--	1.00	1.60	1.50

f_reh_9 _md4

Group	Conc (ppm)	Amt Mtb (nmol/min-g)	N	Effect 1	Effect 2
1	0	0.000	10	0	0
2	0.1	0.912	10	0	0
3	1	4.439	10	10	0
4	10	7.123	10	9	7
5	30	7.548	10	9	6

BMD_{10}	4.99	5.24
$BMDL_{10}$	3.84	3.69

Dodd et al. Scale (1-5): 1= minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe, 5 = severe/high

**Level 2, Transitional respiratory epithelium hyperplasia*

Female RESM Lesions in the Subchronic (90-Day) Dodd et al. (2012) Study

Group	1	2	3	4	5
Amt Mtb (nmol/min-g)	**0**	**0.912448**	**4.438954**	**7.122926**	**7.547781**
Number Examined	10	10	10	10	10
With f_resm lesion*	0	0	0	9	8
Severity 1	0	0	0	9	8
Severity 2	0	0	0	0	0
Severity 3	0	0	0	0	0
Severity 4	0	0	0	0	0
Severity 5	0	0	0	0	0
Average Severity	--	--	--	0.90	0.80

f_resm_9 _md4

Group	Conc (ppm)	Amt Mtb (nmol/min-g)	N	Effect 1	Effect 2
1	0	0.000	10	0	0
2	0.1	0.912	10	0	0
3	1	4.439	10	0	0
4	10	7.123	10	9	0
5	30	7.548	10	8	0

BMD_{10}	4.95	--
$BMDL_{10}$	3.74	--

Dodd et al. Scale (1-5): 1= minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe, 5 = severe/high

**Level 2, Transitional respiratory epithelium squamous metaplasia*

Female OED Lesions in the Subchronic (90-Day) Dodd et al. (2012) Study

Group	1	2	3	4	5
Amt Mtb (nmol/min-g)	**0**	**0.141975**	**1.380519**	**10.21883**	**19.38274**
Number Examined	10	10	10	10	10
With f_oed lesion*	0	0	0	10	10
Severity 1	0	0	0	0	0
Severity 2	0	0	0	7	8
Severity 3	0	0	0	3	2
Severity 4	0	0	0	0	0
Severity 5	0	0	0	0	0
Average Severity	--	--	--	2.30	2.20

f_oed_9 _md4

Group	Conc (ppm)	Amt Mtb (nmol/min-g)	N	Effect 1	Effect 2
1	0	0.000	10	0	0
2	0.1	0.142	10	0	0
3	1	1.381	10	0	0
4	10	10.219	10	10	10
5	30	19.383	10	10	10

BMD_{10}	4.41	4.41
$BMDL_{10}$	1.25	1.25

Dodd et al. Scale (1-5): 1= minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe, 5 = severe/high

**Max severity of Levels 2-5, Olfactory epithelium degeneration*

Female OEH Lesions in the Subchronic (90-Day) Dodd et al. (2012) Study

Group	1	2	3	4	5
Amt Mtb (nmol/min-g)	**0**	**0.141975**	**1.380519**	**10.21883**	**19.38274**
Number Examined	10	10	10	10	10
With f_oeh lesion*	0	0	0	10	10
Severity 1	0	0	0	0	0
Severity 2	0	0	0	10	5
Severity 3	0	0	0	0	5
Severity 4	0	0	0	0	0
Severity 5	0	0	0	0	0
Average Severity	--	--	--	2.00	2.50

f_oeh_9 _md4

Group	Conc (ppm)	Amt Mtb (nmol/min-g)	N	Effect 1	Effect 2
1	0	0.000	10	0	0
2	0.1	0.142	10	0	0
3	1	1.381	10	0	0
4	10	10.219	10	10	10
5	30	19.383	10	10	10

BMD_{10}	4.41	4.41
$BMDL_{10}$	1.25	1.25

Dodd et al. Scale (1-5): 1= minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe, 5 = severe/high

**Max severity of Levels 2-5, Olfactory epithelium hyperplasia*

Notes:

Effect 1 = Incidence of all lesions

Effect 2 = Incidence of lesions having a severity $\geq$ 2.

BMDs = Average BMD (or BMDL) in nmol/min-g tissue

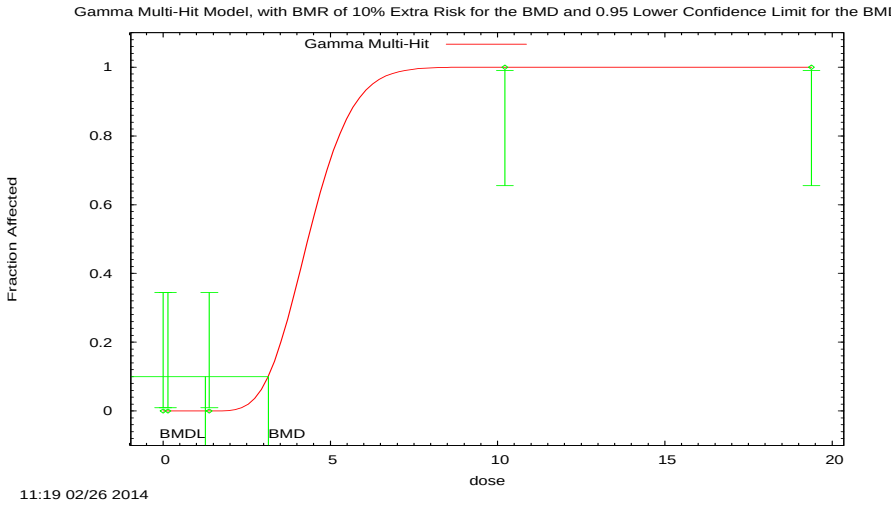
Model Name	Data File Name	Option File Name	AIC	Inputs + Estimates + Scaled Res.	P-value	Specified Effect	Risk Type	BMD	BMDL (POD)	Scaled residual for dose group near BMD	Δ BMD	Δ BMD:POD	Consider Model	POD selected	Selected POD	Average BMD	Average POD	POD Range	N	Model Note
Gamma	f_oed_9_md4.dax	Gam-BMR10.opt	2.00077	Array	1	0.1	Extra risk	3.14545	1.25963	-0.016	1.88582	1.497122	Y	N	--	--	--	--	--	
Logistic	f_oed_9_md4.dax	Log-BMR10.opt	4	Array	1	0.1	Extra risk	5.46189	1.2495	0	4.21239	3.371261	Y	N	--	--	--	--	--	
LogLogistic	f_oed_9_md4.dax	LogLog-BMR10.opt	2	Array	1	0.1	Extra risk	3.36446	1.29844	0	2.06602	1.591156	Y	Y	1.29844	4.4050143	1.2451886	0.20682	7	Selected over Weibull because of smaller delta BMD
Probit	f_oed_9_md4.dax	Probit-BMR10.opt	4	Array	1	0.1	Extra risk	5.26349	1.29435	0	3.96914	3.066512	Y	N	--	--	--	--	--	
LogProbit	f_oed_9_md4.dax	LogPro-BMR10.opt	4	Array	1	0.1	Extra risk	3.54958	1.29456	0	2.25502	1.74192	Y	N	--	--	--	--	--	
Multistage	f_oed_9_md4.dax	NCMst1-BMR10.opt	11.2155	Array	0.269	0.1	Extra risk	0.48343	0.279612	-0.561	0.203816	0.728924	N	N	--	--	--	--	--	Outlier AIC
Multistage	f_oed_9_md4.dax	NCMst2-BMR10.opt	3.84618	Array	0.9169	0.1	Extra risk	1.65623	0.823198	-0.872	0.833032	1.011946	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	f_oed_9_md4.dax	NCMst3-BMR10.opt	2.34613	Array	0.9964	0.1	Extra risk	2.65493	1.09162	-0.387	1.56331	1.432101	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Multistage	f_oed_9_md4.dax	NCMst4-BMR10.opt	2.0602	Array	0.9999	0.1	Extra risk	3.48114	0	-0.162	3.48114	#DIV/0!	N	N	--	--	--	--	--	BMDL = 0
Weibull	f_oed_9_md4.dax	Wei-BMR10.opt	2	Array	1	0.1	Extra risk	7.3953	1.22822	0	6.16708	5.021153	Y	N	--	--	--	--	--	
Quantal-Linear	f_oed_9_md4.dax	Quant-BMR10.opt	11.2155	Array	0.269	0.1	Extra risk	0.48343	0.279612	-0.561	0.203817	0.728928	N	N	--	--	--	--	--	Outlier AIC
Gamma	f_oed_9_sev_md4.dax	Gam-BMR10.opt	2.00077	Array	1	0.1	Extra risk	3.14545	1.25963	-0.016	1.88582	1.497122	Y	N	--	--	--	--	--	
Logistic	f_oed_9_sev_md4.dax	Log-BMR10.opt	4	Array	1	0.1	Extra risk	5.46189	1.2495	0	4.21239	3.371261	Y	N	--	--	--	--	--	
LogLogistic	f_oed_9_sev_md4.dax	LogLog-BMR10.opt	2	Array	1	0.1	Extra risk	3.36446	1.29844	0	2.06602	1.591156	Y	Y	1.29844	4.4050143	1.2451886	0.20682	7	Selected over Weibull for POD because of smaller delta BMD
Probit	f_oed_9_sev_md4.dax	Probit-BMR10.opt	4	Array	1	0.1	Extra risk	5.26349	1.29435	0	3.96914	3.066512	Y	N	--	--	--	--	--	
LogProbit	f_oed_9_sev_md4.dax	LogPro-BMR10.opt	4	Array	1	0.1	Extra risk	3.54958	1.29456	0	2.25502	1.74192	Y	N	--	--	--	--	--	
Multistage	f_oed_9_sev_md4.dax	NCMst1-BMR10.opt	11.2155	Array	0.269	0.1	Extra risk	0.48343	0.279612	-0.561	0.203816	0.728924	N	N	--	--	--	--	--	Outlier AIC
Multistage	f_oed_9_sev_md4.dax	NCMst2-BMR10.opt	3.84618	Array	0.9169	0.1	Extra risk	1.65623	0.823198	-0.872	0.833032	1.011946	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	f_oed_9_sev_md4.dax	NCMst3-BMR10.opt	2.34613	Array	0.9964	0.1	Extra risk	2.65493	1.09162	-0.387	1.56331	1.432101	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Multistage	f_oed_9_sev_md4.dax	NCMst4-BMR10.opt	2.0602	Array	0.9999	0.1	Extra risk	3.48114	0	-0.162	3.48114	#DIV/0!	N	N	--	--	--	--	--	BMDL = 0
Weibull	f_oed_9_sev_md4.dax	Wei-BMR10.opt	2	Array	1	0.1	Extra risk	7.3953	1.22822	0	6.16708	5.021153	Y	N	--	--	--	--	--	
Quantal-Linear	f_oed_9_sev_md4.dax	Quant-BMR10.opt	11.2155	Array	0.269	0.1	Extra risk	0.48343	0.279612	-0.561	0.203817	0.728928	N	N	--	--	--	--	--	Outlier AIC
Gamma	f_oeh_9_md4.dax	Gam-BMR10.opt	2.00077	Array	1	0.1	Extra risk	3.14545	1.25963	-0.016	1.88582	1.497122	Y	N	--	--	--	--	--	
Logistic	f_oeh_9_md4.dax	Log-BMR10.opt	4	Array	1	0.1	Extra risk	5.46189	1.2495	0	4.21239	3.371261	Y	N	--	--	--	--	--	
LogLogistic	f_oeh_9_md4.dax	LogLog-BMR10.opt	2	Array	1	0.1	Extra risk	3.36446	1.29844	0	2.06602	1.591156	Y	Y	1.29844	4.4050143	1.2451886	0.20682	7	Selected over Weibull because of smaller delta BMD
Probit	f_oeh_9_md4.dax	Probit-BMR10.opt	4	Array	1	0.1	Extra risk	5.26349	1.29435	0	3.96914	3.066512	Y	N	--	--	--	--	--	
LogProbit	f_oeh_9_md4.dax	LogPro-BMR10.opt	4	Array	1	0.1	Extra risk	3.54958	1.29456	0	2.25502	1.74192	Y	N	--	--	--	--	--	
Multistage	f_oeh_9_md4.dax	NCMst1-BMR10.opt	11.2155	Array	0.269	0.1	Extra risk	0.48343	0.279612	-0.561	0.203816	0.728924	N	N	--	--	--	--	--	Outlier AIC
Multistage	f_oeh_9_md4.dax	NCMst2-BMR10.opt	3.84618	Array	0.9169	0.1	Extra risk	1.65623	0.823198	-0.872	0.833032	1.011946	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	f_oeh_9_md4.dax	NCMst3-BMR10.opt	2.34613	Array	0.9964	0.1	Extra risk	2.65493	1.09162	-0.387	1.56331	1.432101	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Multistage	f_oeh_9_md4.dax	NCMst4-BMR10.opt	2.0602	Array	0.9999	0.1	Extra risk	3.48114	0	-0.162	3.48114	#DIV/0!	N	N	--	--	--	--	--	BMDL = 0
Weibull	f_oeh_9_md4.dax	Wei-BMR10.opt	2	Array	1	0.1	Extra risk	7.3953	1.22822	0	6.16708	5.021153	Y	N	--	--	--	--	--	
Quantal-Linear	f_oeh_9_md4.dax	Quant-BMR10.opt	11.2155	Array	0.269	0.1	Extra risk	0.48343	0.279612	-0.561	0.203817	0.728928	N	N	--	--	--	--	--	Outlier AIC

Model Name	Data File Name	Option File Name	AIC	Inputs + Estimates + Scaled Res.	P-value	Specified Effect	Risk Type	BMD	BMDL (POD)	Scaled residual for dose group near BMD	Δ BMD	Δ BMD:POD	Consider Model	POD selected	Selected POD	Average BMD	Average POD	POD Range	N	Model Note
Gamma	f_oeh_9_sev_md4.dax	Gam-BMR10.opt	2.00077	Array	1	0.1	Extra risk	3.14545	1.25963	-0.016	1.88582	1.497122	Y	N	--	--	--	--	--	
Logistic	f_oeh_9_sev_md4.dax	Log-BMR10.opt	4	Array	1	0.1	Extra risk	5.46189	1.2495	0	4.21239	3.371261	Y	N	--	--	--	--	--	
LogLogistic	f_oeh_9_sev_md4.dax	LogLog-BMR10.opt	2	Array	1	0.1	Extra risk	3.36446	1.29844	0	2.06602	1.591156	Y	Y	1.29844	4.4050143	1.2451886	0.20682	7	Selected over Weibull because of smaller delta BMD
Probit	f_oeh_9_sev_md4.dax	Probit-BMR10.opt	4	Array	1	0.1	Extra risk	5.26349	1.29435	0	3.96914	3.066512	Y	N	--	--	--	--	--	
LogProbit	f_oeh_9_sev_md4.dax	LogPro-BMR10.opt	4	Array	1	0.1	Extra risk	3.54958	1.29456	0	2.25502	1.74192	Y	N	--	--	--	--	--	
Multistage	f_oeh_9_sev_md4.dax	NCMst1-BMR10.opt	11.2155	Array	0.269	0.1	Extra risk	0.48343	0.279612	-0.561	0.203816	0.728924	N	N	--	--	--	--	--	Outlier AIC
Multistage	f_oeh_9_sev_md4.dax	NCMst2-BMR10.opt	3.84618	Array	0.9169	0.1	Extra risk	1.65623	0.823198	-0.872	0.833032	1.011946	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	f_oeh_9_sev_md4.dax	NCMst3-BMR10.opt	2.34613	Array	0.9964	0.1	Extra risk	2.65493	1.09162	-0.387	1.56331	1.432101	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Multistage	f_oeh_9_sev_md4.dax	NCMst4-BMR10.opt	2.0602	Array	0.9999	0.1	Extra risk	3.48114	0	-0.162	3.48114	#DIV/0!	N	N	--	--	--	--	--	BMDL = 0
Weibull	f_oeh_9_sev_md4.dax	Wei-BMR10.opt	2	Array	1	0.1	Extra risk	7.3953	1.22822	0	6.16708	5.021153	Y	N	--	--	--	--	--	
Quantal-Linear	f_oeh_9_sev_md4.dax	Quant-BMR10.opt	11.2155	Array	0.269	0.1	Extra risk	0.48343	0.279612	-0.561	0.203817	0.728928	N	N	--	--	--	--	--	Outlier AIC
Gamma	f_reh_9_md4.dax	Gam-BMR10.opt	18.6355	Array	0.7012	0.1	Extra risk	4.2322	3.61273	-1.254	0.61947	0.171469	Y	N	--	--	--	--	--	
Logistic	f_reh_9_md4.dax	Log-BMR10.opt	17.6354	Array	0.896	0.1	Extra risk	5.55254	4.12764	-0.261	1.4249	0.345209	Y	N	--	--	--	--	--	
LogLogistic	f_reh_9_md4.dax	LogLog-BMR10.opt	17.4376	Array	0.9387	0.1	Extra risk	5.47818	4.22496	-0.212	1.25322	0.296623	Y	N	--	--	--	--	--	
Probit	f_reh_9_md4.dax	Probit-BMR10.opt	17.6518	Array	0.8907	0.1	Extra risk	5.413	4.15537	-0.221	1.25763	0.302652	Y	N	--	--	--	--	--	
LogProbit	f_reh_9_md4.dax	LogPro-BMR10.opt	17.4339	Array	0.9377	0.1	Extra risk	5.32694	4.25348	-0.173	1.07346	0.252372	Y	Y	4.25348	4.9867857	3.8426929	1.68466	7	
Multistage	f_reh_9_md4.dax	NCMst1-BMR10.opt	37.0266	Array	0.0033	0.1	Extra risk	0.71739	0.487642	-1.197	0.229749	0.471143	N	N	--	--	--	--	--	P-value too low
Multistage	f_reh_9_md4.dax	NCMst2-BMR10.opt	28.5214	Array	0.0548	0.1	Extra risk	2.00544	1.32384	-0.469	0.6816	0.514866	N	N	--	--	--	--	--	P-value too low
Multistage	f_reh_9_md4.dax	NCMst3-BMR10.opt	23.743	Array	0.2309	0.1	Extra risk	2.92732	2.03673	-2.107	0.89059	0.437265	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	f_reh_9_md4.dax	NCMst4-BMR10.opt	20.6867	Array	0.4879	0.1	Extra risk	3.58209	2.56882	-1.679	1.01327	0.39445	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Weibull	f_reh_9_md4.dax	Wei-BMR10.opt	18.2771	Array	0.7725	0.1	Extra risk	5.32255	3.95585	-0.433	1.3667	0.345488	Y	N	--	--	--	--	--	
Quantal-Linear	f_reh_9_md4.dax	Quant-BMR10.opt	37.0266	Array	0.0033	0.1	Extra risk	0.71739	0.487642	-1.197	0.229749	0.471143	N	N	--	--	--	--	--	P-value too low
Gamma	f_reh_9_sev_md4.dax	Gam-BMR10.opt	29.4993	Array	0.8539	0.1	Extra risk	4.94638	3.77618	-0.694	1.1702	0.30989	Y	Y	3.77618	5.2434329	3.6892457	1.23229	7	
Logistic	f_reh_9_sev_md4.dax	Log-BMR10.opt	31.4582	Array	0.6567	0.1	Extra risk	5.56791	3.83714	-0.432	1.73077	0.451057	Y	N	--	--	--	--	--	
LogLogistic	f_reh_9_sev_md4.dax	LogLog-BMR10.opt	31.1002	Array	0.7292	0.1	Extra risk	5.50933	3.90306	-0.366	1.60627	0.411541	Y	N	--	--	--	--	--	
Probit	f_reh_9_sev_md4.dax	Probit-BMR10.opt	31.2172	Array	0.6966	0.1	Extra risk	5.54104	3.8423	-0.333	1.69874	0.442115	Y	N	--	--	--	--	--	
LogProbit	f_reh_9_sev_md4.dax	LogPro-BMR10.opt	30.8944	Array	0.7658	0.1	Extra risk	5.45736	4.02849	-0.274	1.42887	0.354691	Y	N	--	--	--	--	--	
Multistage	f_reh_9_sev_md4.dax	NCMst1-BMR10.opt	39.8662	Array	0.0798	0.1	Extra risk	1.19595	0.775455	-0.915	0.420495	0.542256	N	N	--	--	--	--	--	P-value too low
Multistage	f_reh_9_sev_md4.dax	NCMst2-BMR10.opt	35.0201	Array	0.3134	0.1	Extra risk	2.68381	1.58781	-1.828	1.096	0.690259	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	f_reh_9_sev_md4.dax	NCMst3-BMR10.opt	32.5272	Array	0.5474	0.1	Extra risk	3.6241	2.29912	-1.462	1.32498	0.576299	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	f_reh_9_sev_md4.dax	NCMst4-BMR10.opt	31.0701	Array	0.6997	0.1	Extra risk	4.25519	2.7962	-1.153	1.45899	0.521776	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Weibull	f_reh_9_sev_md4.dax	Wei-BMR10.opt	31.6192	Array	0.6345	0.1	Extra risk	5.42682	3.64135	-0.488	1.78547	0.490332	Y	N	--	--	--	--	--	
Quantal-Linear	f_reh_9_sev_md4.dax	Quant-BMR10.opt	39.8662	Array	0.0798	0.1	Extra risk	1.19595	0.775455	-0.915	0.420495	0.542256	N	N	--	--	--	--	--	P-value too low
Gamma	f_resm_9_md4.dax	Gam-BMR10.opt	22.1517	Array	0.6703	0.1	Extra risk	4.39044	3.66306	-1.098	0.72738	0.198572	Y	N	--	--	--	--	--	
Logistic	f_resm_9_md4.dax	Log-BMR10.opt	22.5618	Array	0.5813	0.1	Extra risk	5.40146	3.94131	-0.396	1.46015	0.370473	Y	N	--	--	--	--	--	

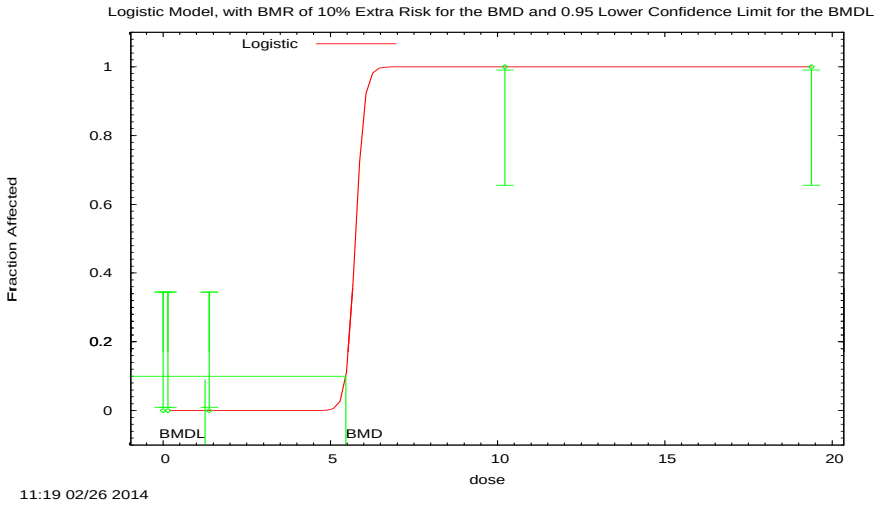
Model Name	Data File Name	Option File Name	AIC	Inputs + Estimates + Scaled Res.	P-value	Specified Effect	Risk Type	BMD	BMDL (POD)	Scaled residual for dose group near BMD	Δ BMD	Δ BMD:POD	Consider Model	POD selected	Selected POD	Average BMD	Average POD	POD Range	N	Model Note
LogLogistic	f_resm_9_md4.dax	LogLog-BMR10.opt	22.1805	Array	0.6611	0.1	Extra risk	5.34033	4.09242	-0.335	1.24791	0.304932	Y	N	--	--	--	--	--	
Probit	f_resm_9_md4.dax	Probit-BMR10.opt	22.5244	Array	0.5908	0.1	Extra risk	5.32946	3.9892	-0.33	1.34026	0.335972	Y	N	--	--	--	--	--	
LogProbit	f_resm_9_md4.dax	LogPro-BMR10.opt	22.1299	Array	0.6721	0.1	Extra risk	5.25288	4.15165	-0.272	1.10123	0.265251	Y	Y	4.15165	4.9475843	3.7424486	1.54091	7	
Multistage	f_resm_9_md4.dax	NCMst1-BMR10.opt	38.2781	Array	0.0072	0.1	Extra risk	0.79352	0.535982	-1.135	0.257539	0.480499	N	N	--	--	--	--	--	P-value too low
Multistage	f_resm_9_md4.dax	NCMst2-BMR10.opt	30.7641	Array	0.0828	0.1	Extra risk	2.13255	1.37373	-0.441	0.75882	0.552379	N	N	--	--	--	--	--	P-value too low
Multistage	f_resm_9_md4.dax	NCMst3-BMR10.opt	26.6909	Array	0.2649	0.1	Extra risk	3.07082	2.08712	-1.936	0.9837	0.471319	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	f_resm_9_md4.dax	NCMst4-BMR10.opt	24.1919	Array	0.4672	0.1	Extra risk	3.73118	2.61074	-1.533	1.12044	0.429166	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Weibull	f_resm_9_md4.dax	Wei-BMR10.opt	23.2617	Array	0.4918	0.1	Extra risk	5.18734	3.74876	-0.547	1.43858	0.383748	Y	N	--	--	--	--	--	
Quantal-Linear	f_resm_9_md4.dax	Quant-BMR10.opt	38.2781	Array	0.0072	0.1	Extra risk	0.79352	0.535982	-1.135	0.257539	0.480499	N	N	--	--	--	--	--	P-value too low
Gamma	f_resm_9_sev_md4.dax	Gam-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Logistic	f_resm_9_sev_md4.dax	Log-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
LogLogistic	f_resm_9_sev_md4.dax	LogLog-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Probit	f_resm_9_sev_md4.dax	Probit-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
LogProbit	f_resm_9_sev_md4.dax	LogPro-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Multistage	f_resm_9_sev_md4.dax	NCMst1-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Multistage	f_resm_9_sev_md4.dax	NCMst2-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Multistage	f_resm_9_sev_md4.dax	NCMst3-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Multistage	f_resm_9_sev_md4.dax	NCMst4-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Weibull	f_resm_9_sev_md4.dax	Wei-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Quantal-Linear	f_resm_9_sev_md4.dax	Quant-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS

Model excluded from average
Reason for model exclusion
Selected model (best fit)

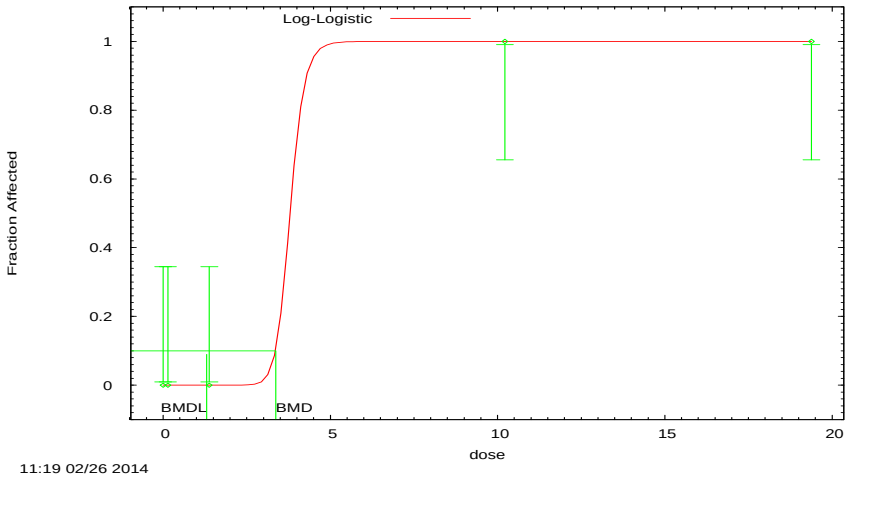
A: Gamma_f_oed_9_md4_Gam-BMR10



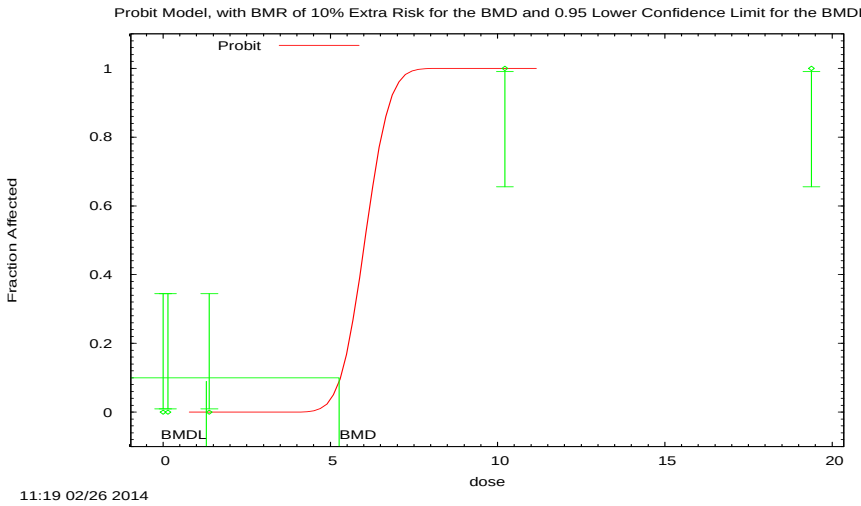
B: Logistic_f_oed_9_md4_Log-BMR10



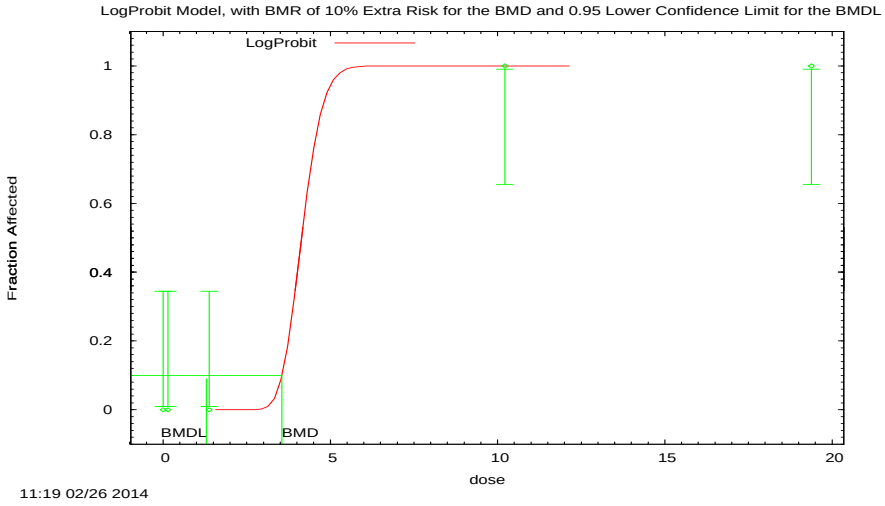
C: LogLogistic_f_oed_9_md4_LogLog-BMR10



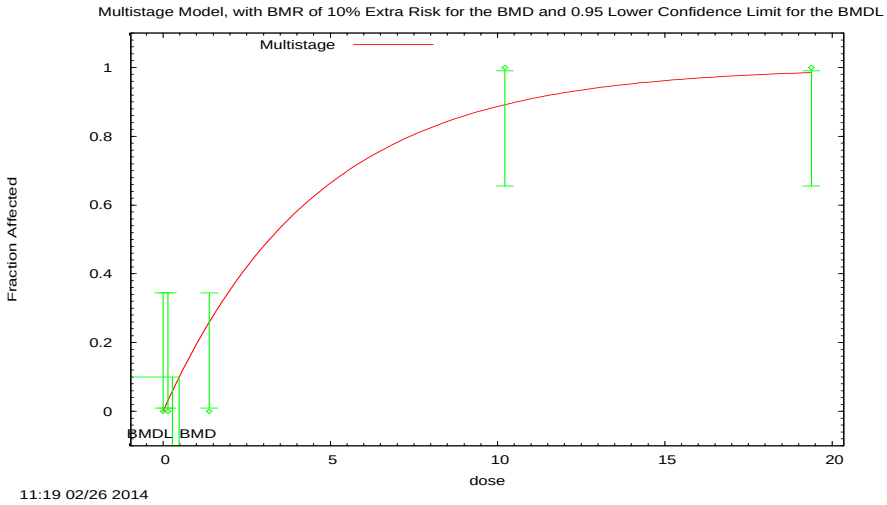
D: Probit_f_oed_9_md4_Probit-BMR10



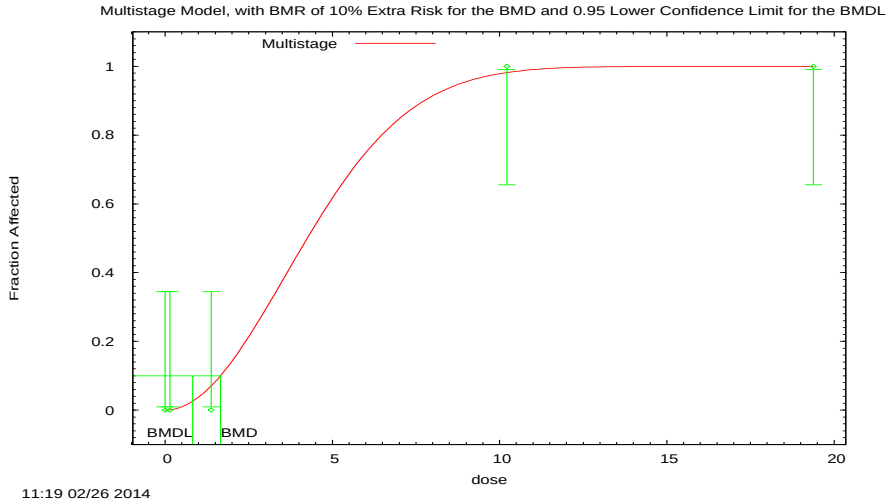
E: LogProbit_f_oed_9_md4_LogPro-BMR10



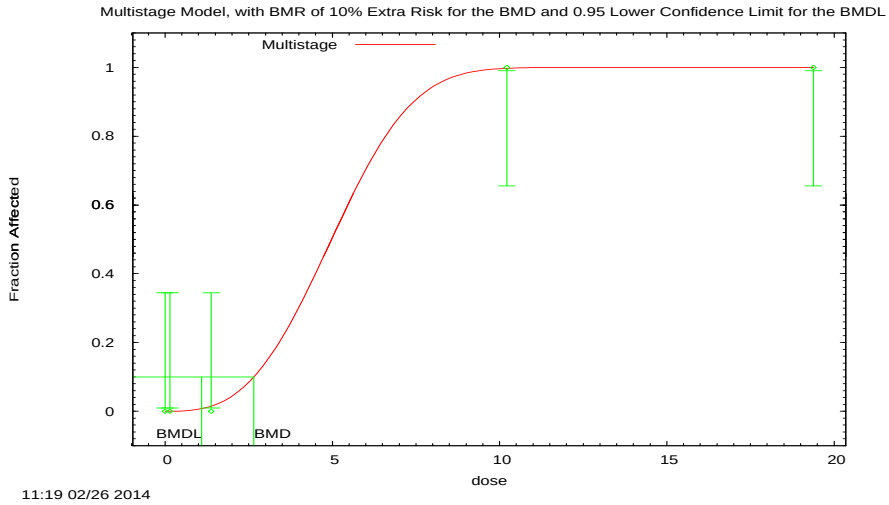
F: Multistage_f_oed_9_md4_NCMst1-BMR10



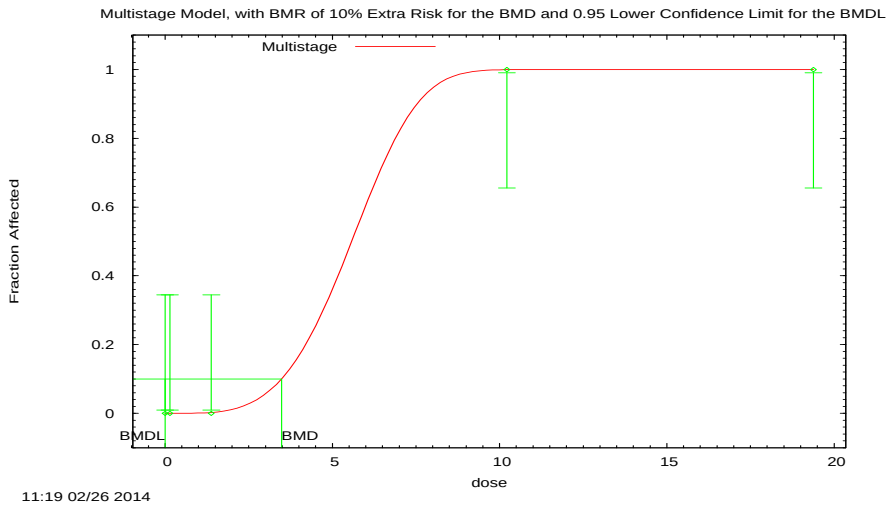
G: Multistage_f_oed_9_md4_NCMst2-BMR10



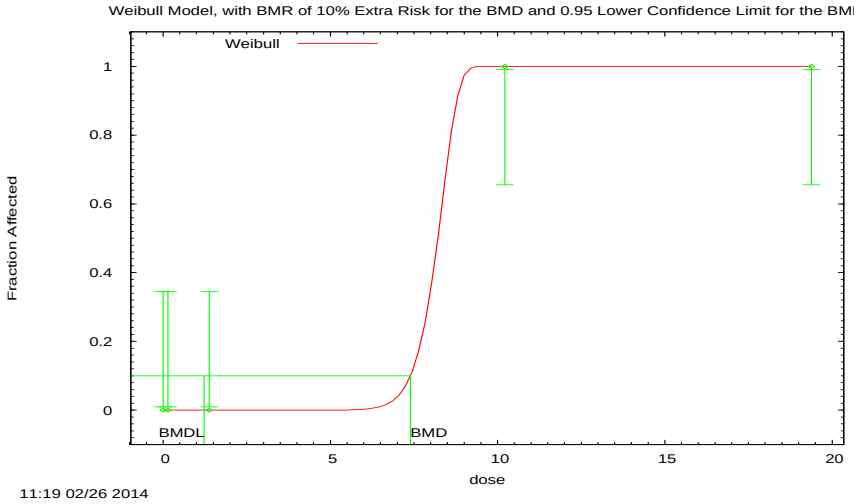
H: Multistage_f_oed_9_md4_NCMst3-BMR10



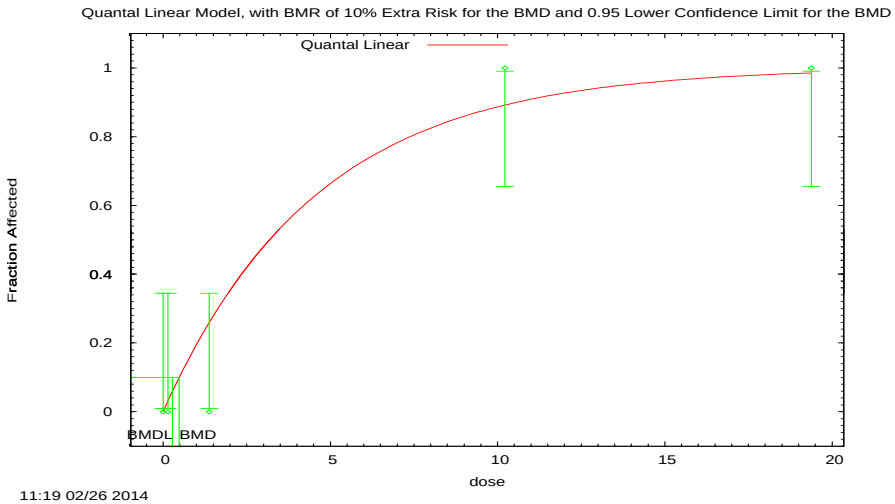
I: Multistage_f_oed_9_md4_NCMst4-BMR10



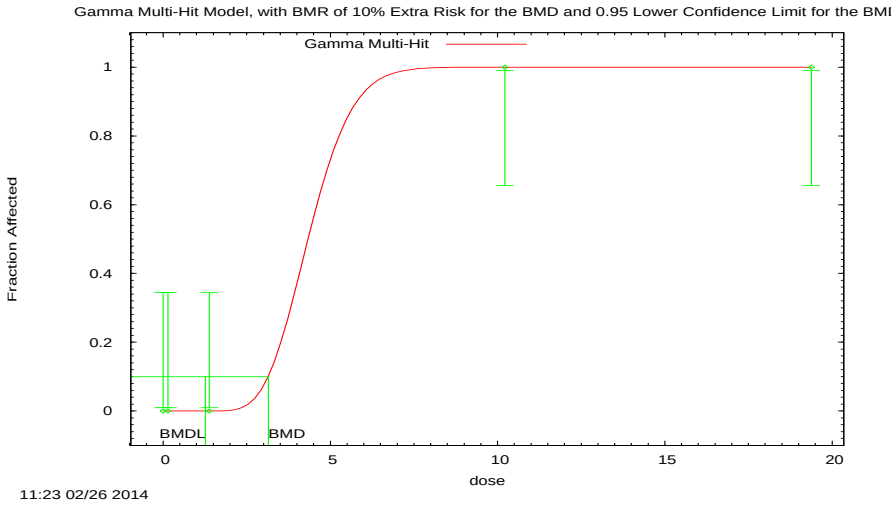
J: Weibull_f_oed_9_md4_Wei-BMR10



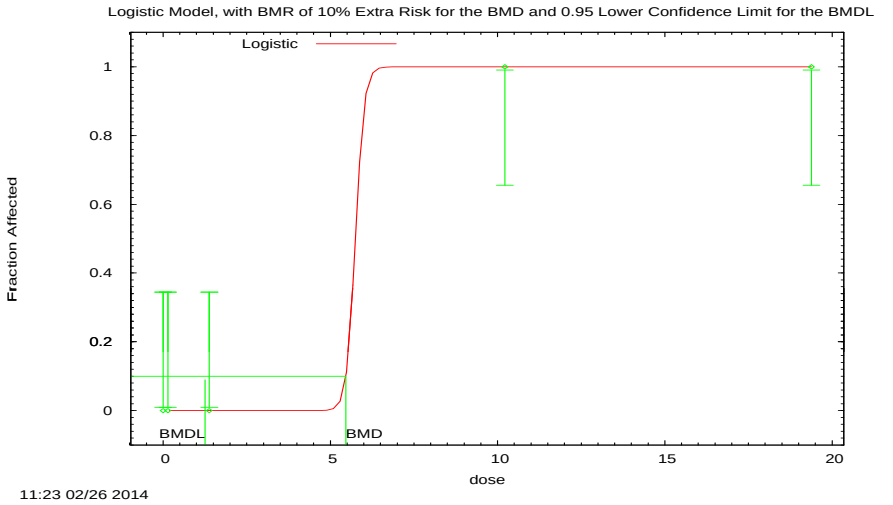
K: Quantal-Linear_f_oed_9_md4_Quant-BMR10



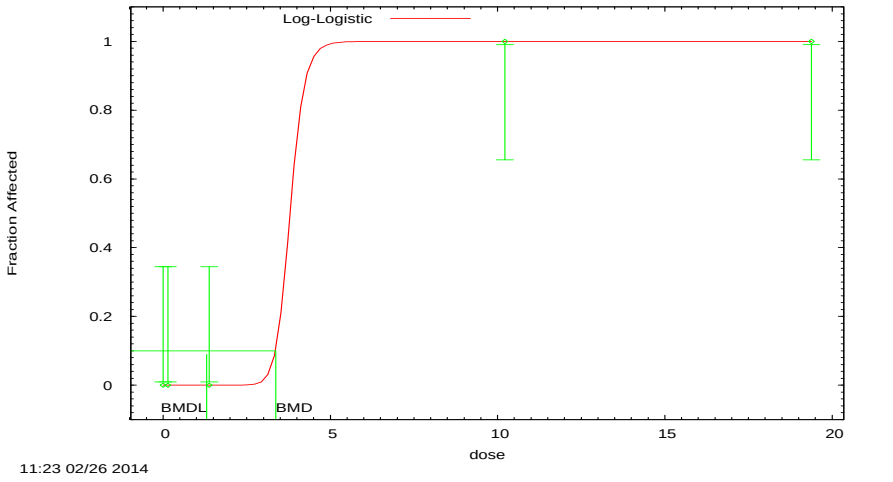
A: Gamma_f_oeh_9_md4_Gam-BMR10



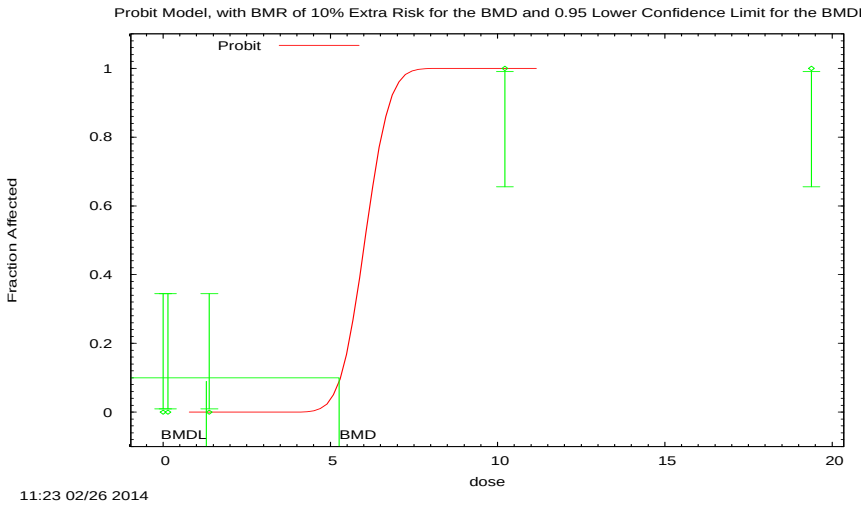
B: Logistic_f_oeh_9_md4_Log-BMR10



C: LogLogistic_f_oeh_9_md4_LogLog-BMR10



D: Probit_f_oeh_9_md4_Probit-BMR10



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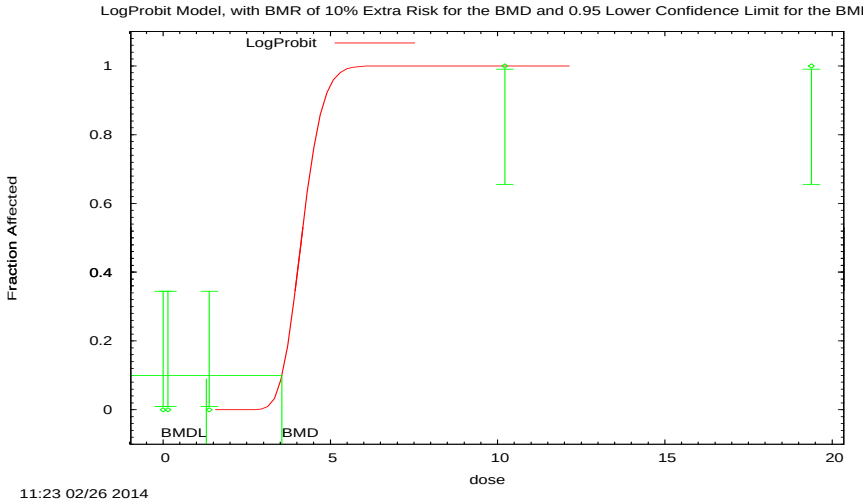
E: LogProbit_f_oeh_9_md4_LogPro-BMR10



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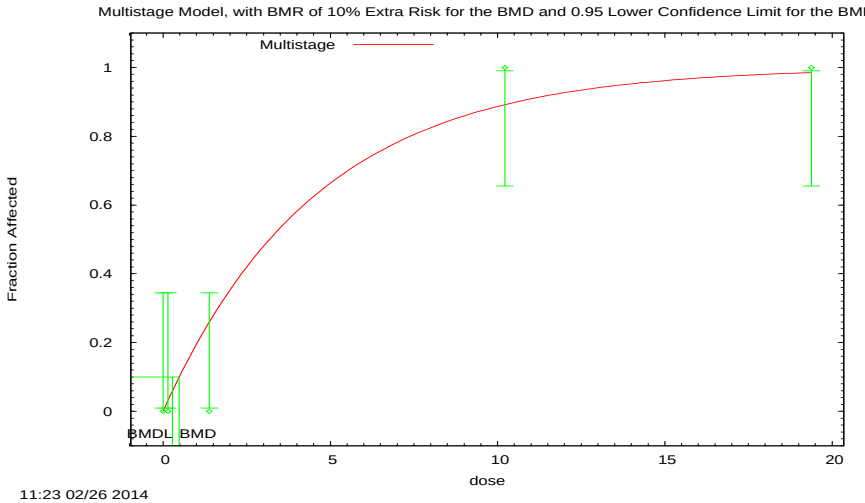
F: Multistage_f_oeh_9_md4_NCMst1-BMR10



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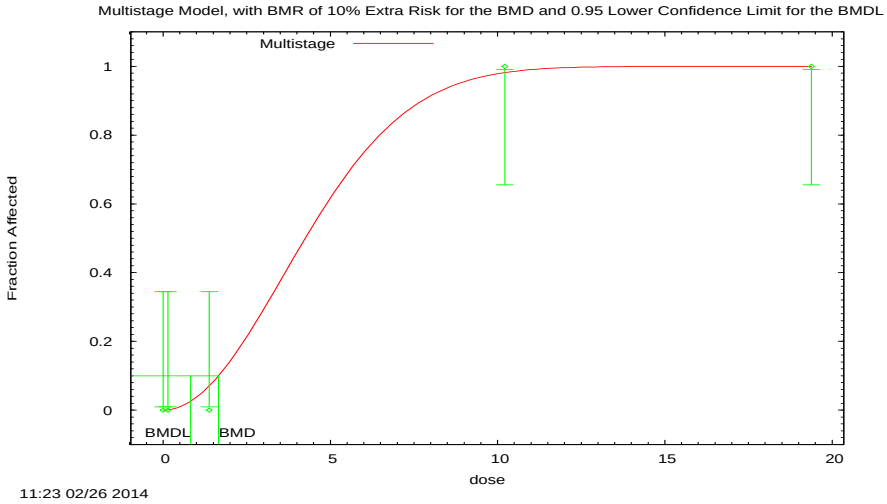
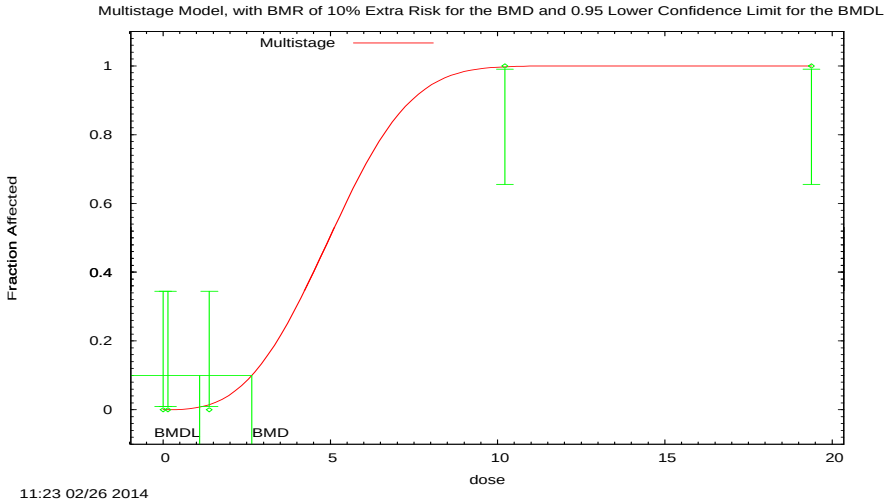
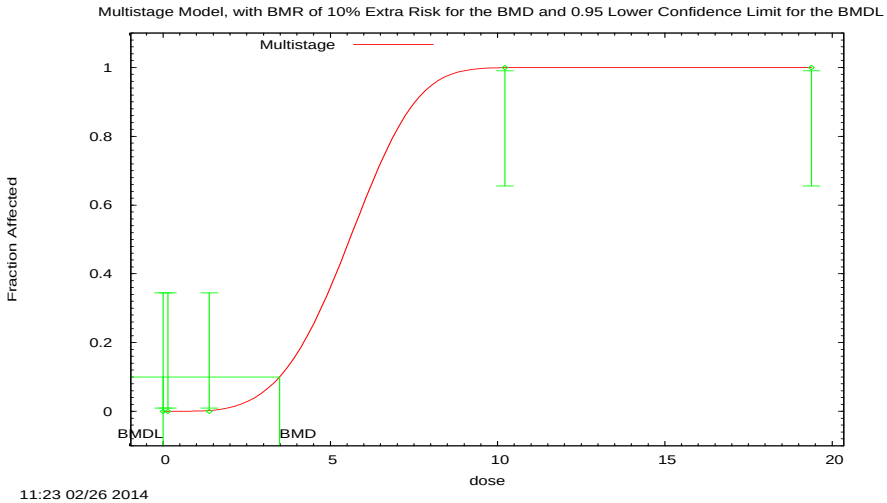
G: Multistage_f_oeh_9_md4_NCMst2-BMR10



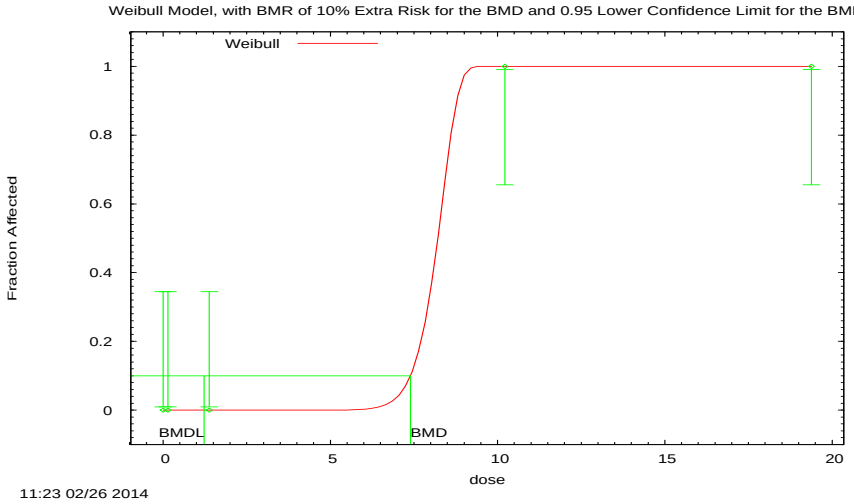
H: Multistage_f_oeh_9_md4_NCMst3-BMR10



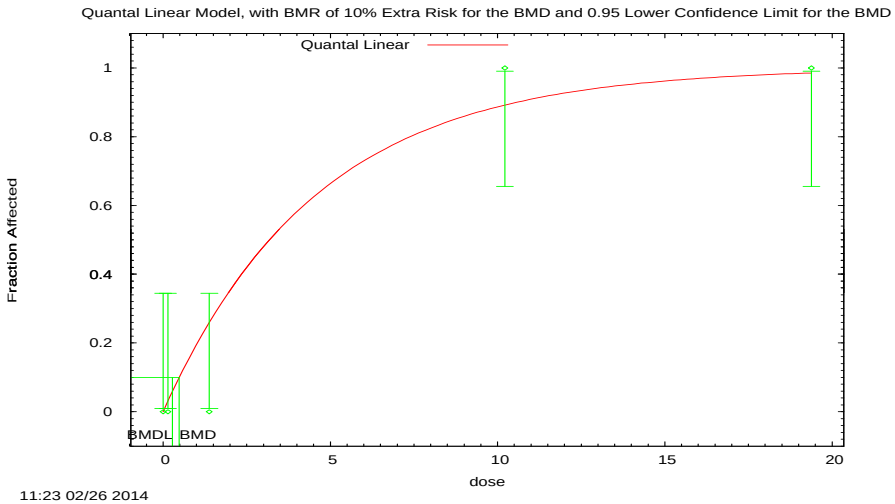
I: Multistage_f_oeh_9_md4_NCMst4-BMR10



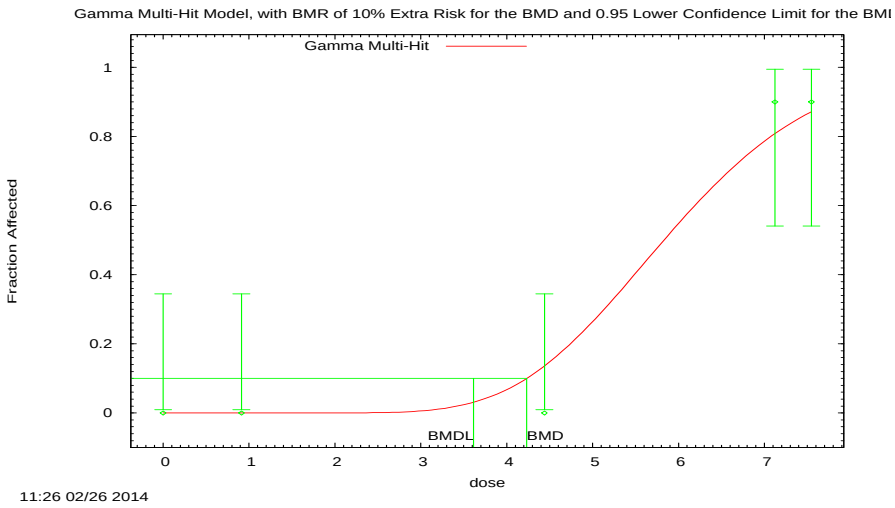
J: Weibull_f_oeh_9_md4_Wei-BMR10



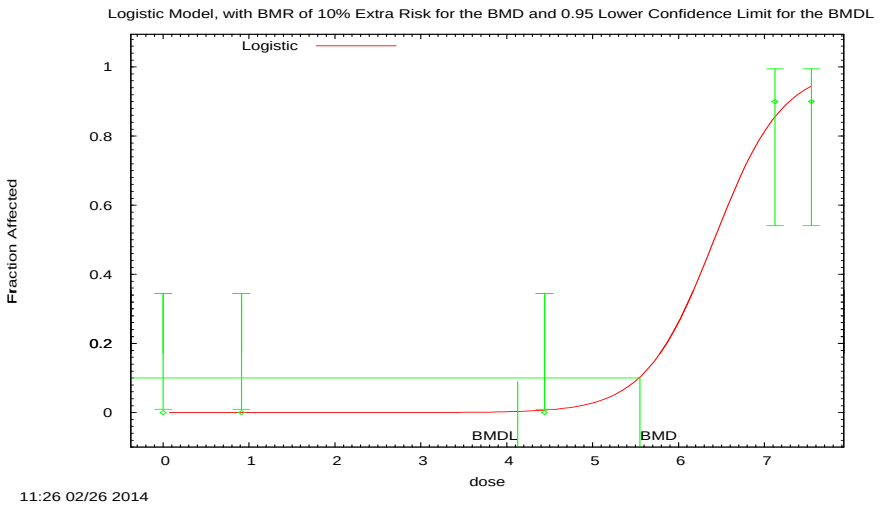
K: Quantal-Linear_f_oeh_9_md4_Quant-BMR10



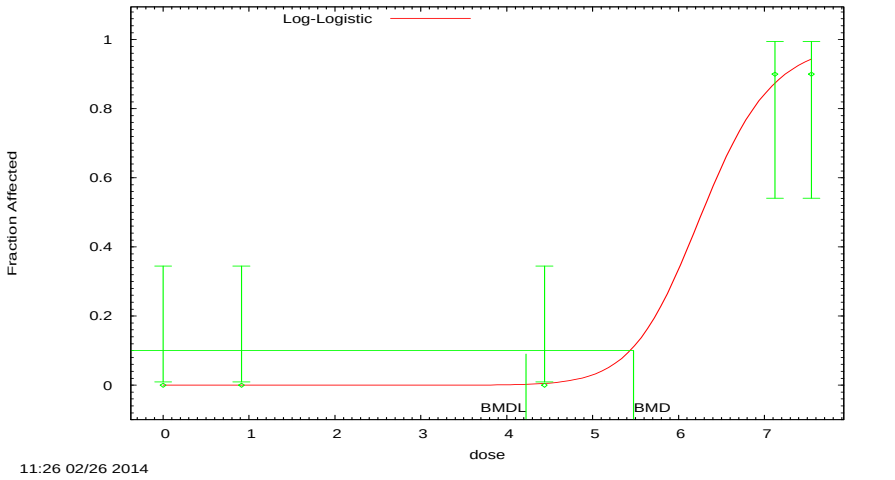
A: Gamma_f_reh_9_md4_Gam-BMR10



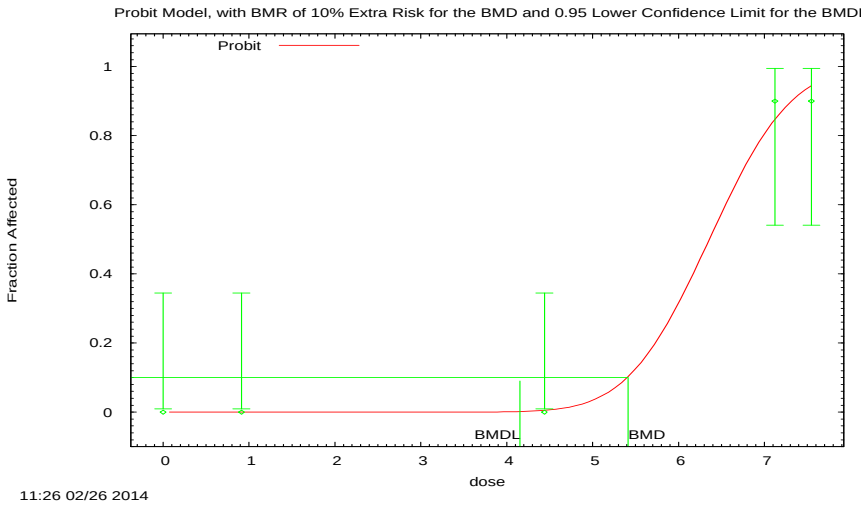
B: Logistic_f_reh_9_md4_Log-BMR10



C: LogLogistic_f_reh_9_md4_LogLog-BMR10



D: Probit_f_reh_9_md4_Probit-BMR10



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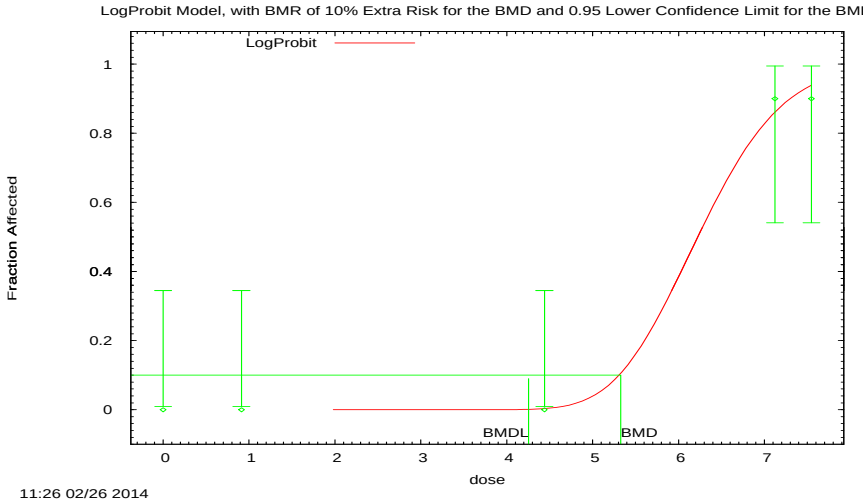
E: LogProbit_f_reh_9_md4_LogPro-BMR10



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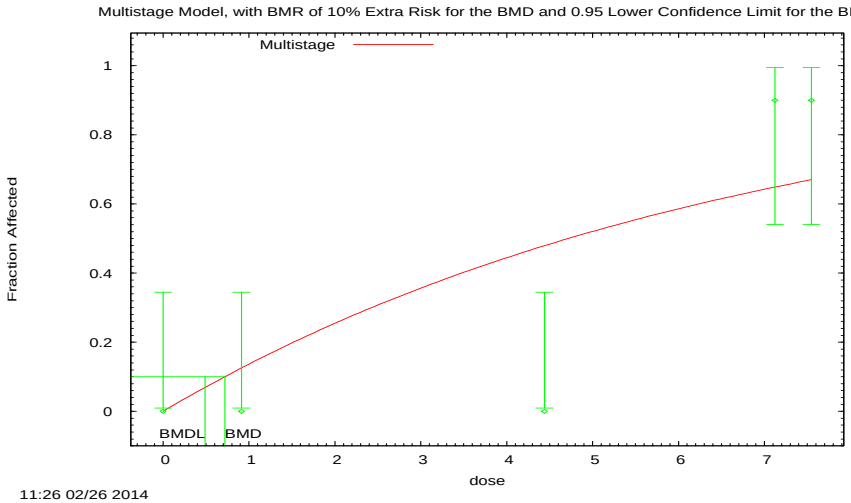
F: Multistage_f_reh_9_md4_NCMst1-BMR10



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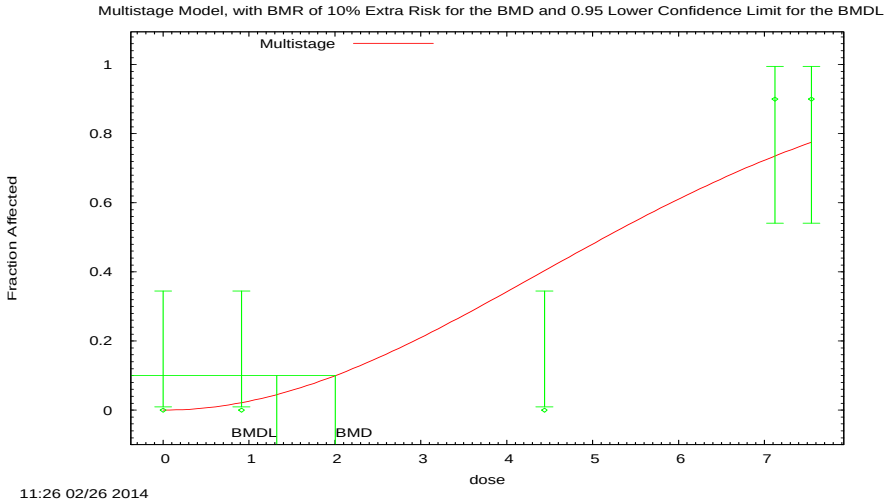
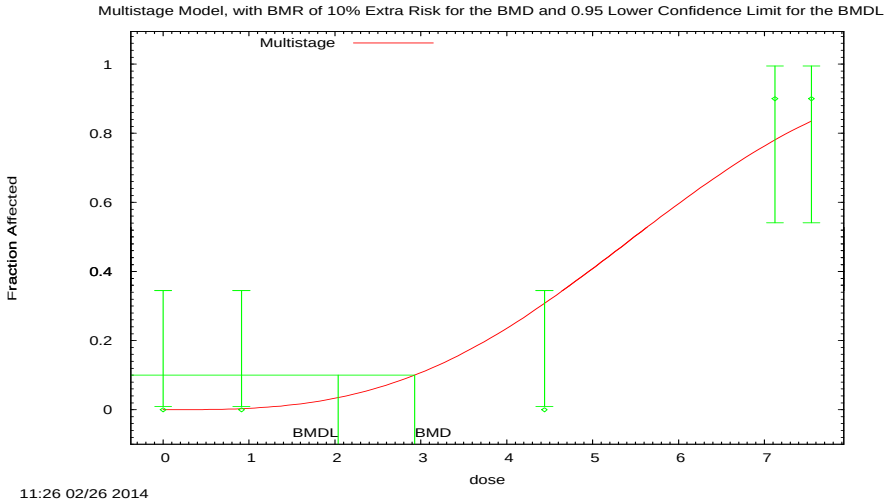
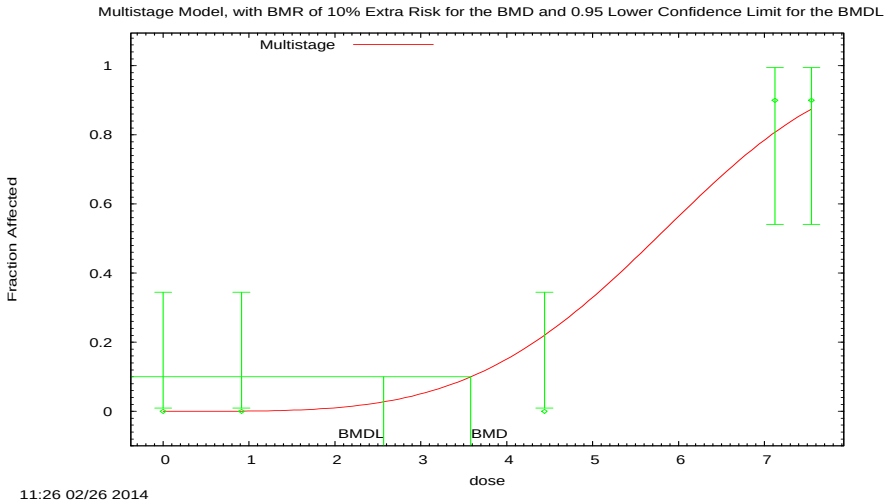
G: Multistage_f_reh_9_md4_NCMst2-BMR10



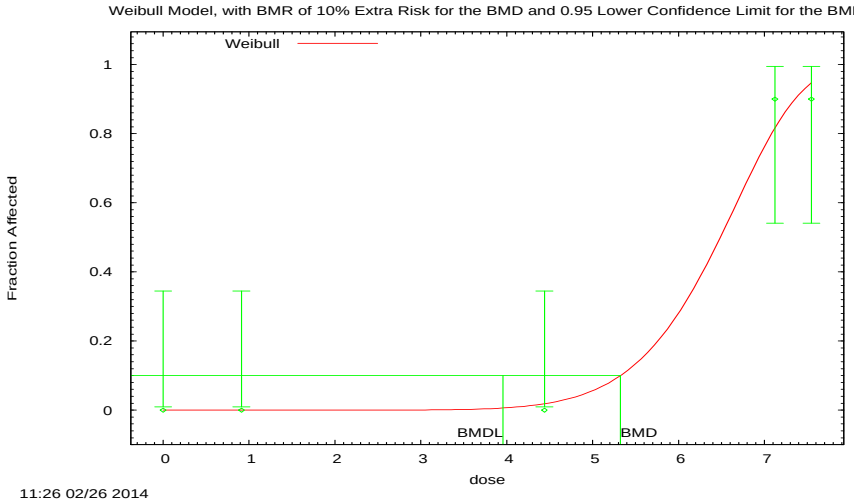
H: Multistage_f_reh_9_md4_NCMst3-BMR10



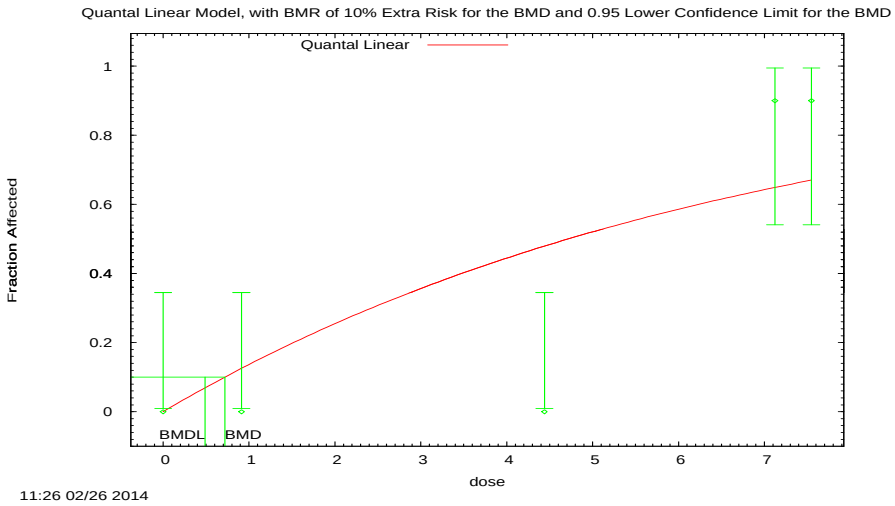
I: Multistage_f_reh_9_md4_NCMst4-BMR10



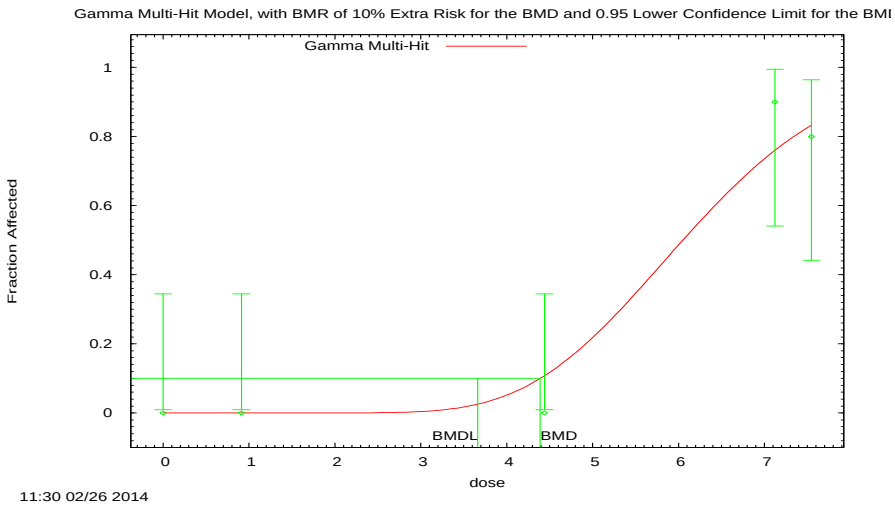
J: Weibull_f_reh_9_md4_Wei-BMR10



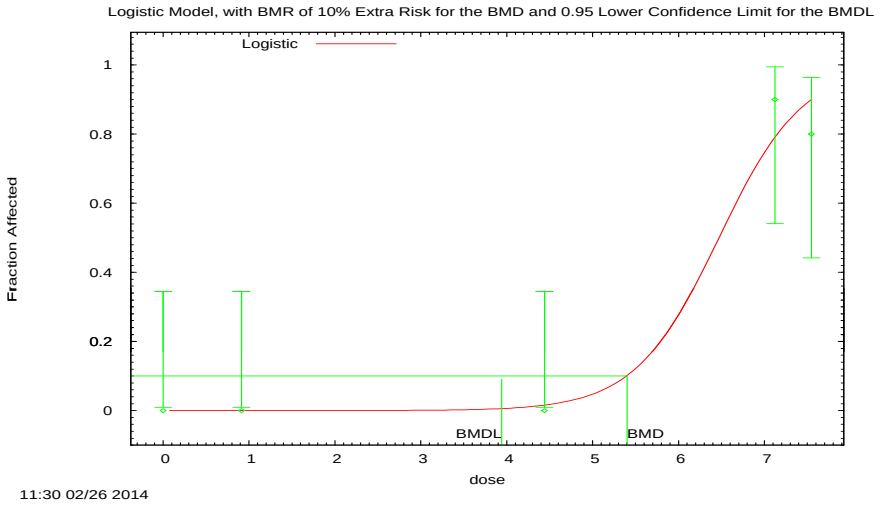
K: Quantal-Linear_f_reh_9_md4_Quant-BMR10



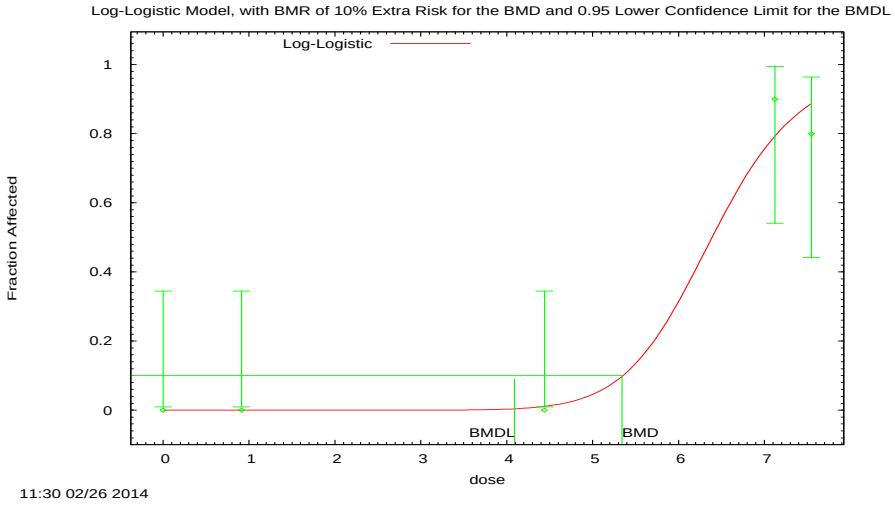
A: Gamma_f_resm_9_md4_Gam-BMR10



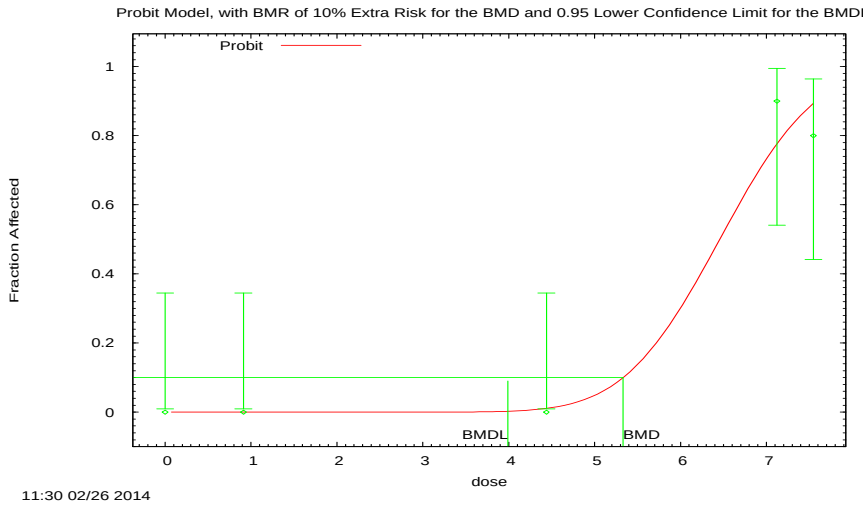
B: Logistic_f_resm_9_md4_Log-BMR10



C: LogLogistic_f_resm_9_md4_LogLog-BMR10



D: Probit_f_resm_9_md4_Probit-BMR10



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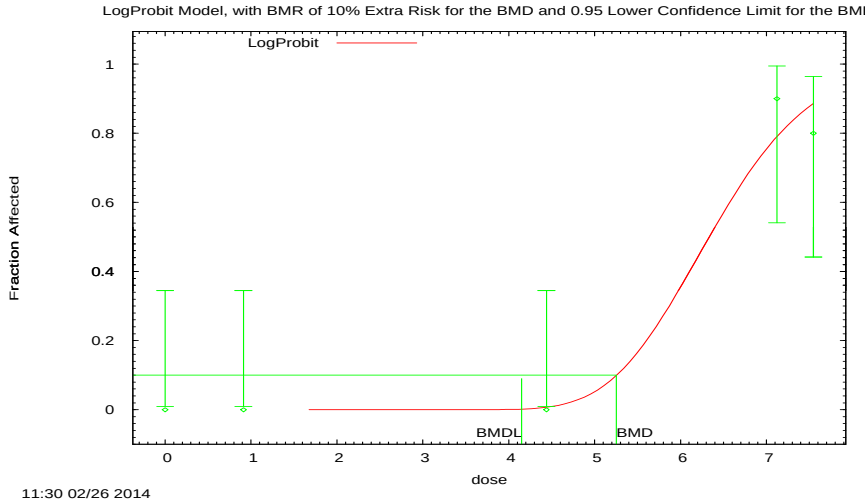
E: LogProbit_f_resm_9_md4_LogPro-BMR10



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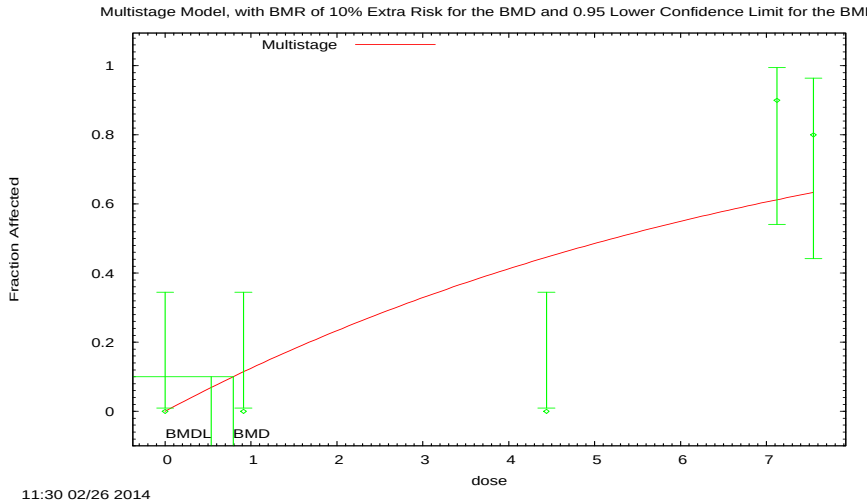
F: Multistage_f_resm_9_md4_NCMst1-BMR10



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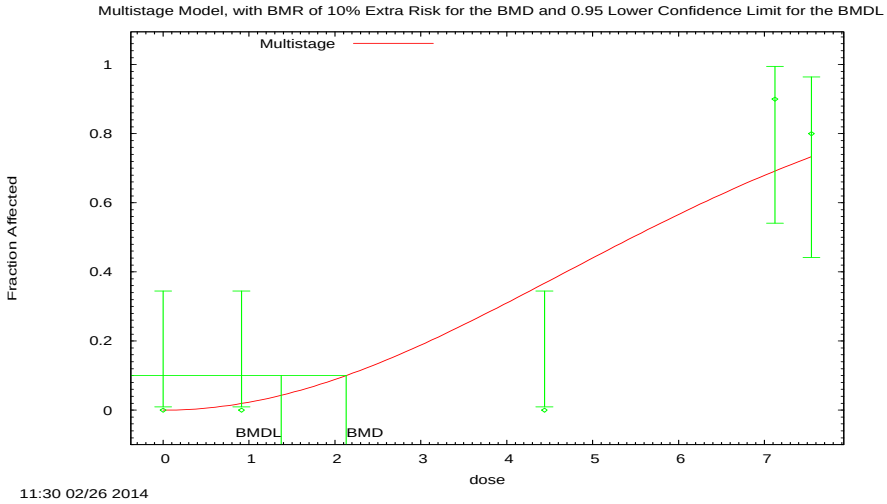
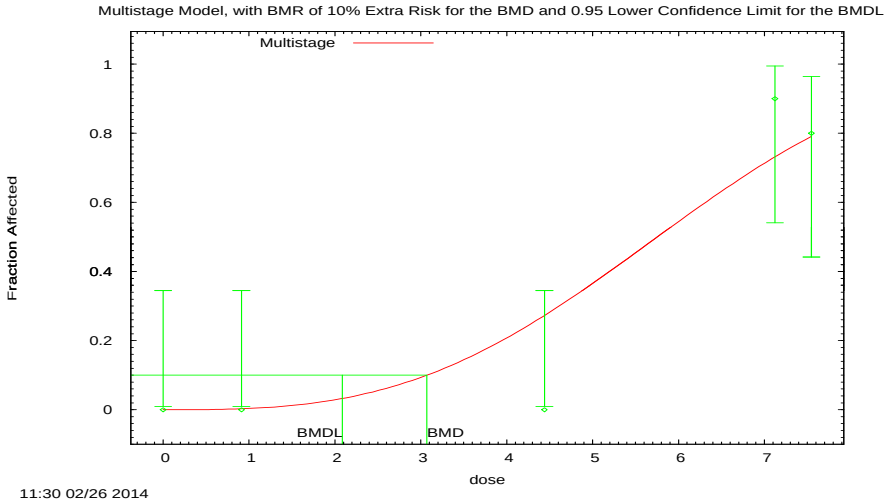
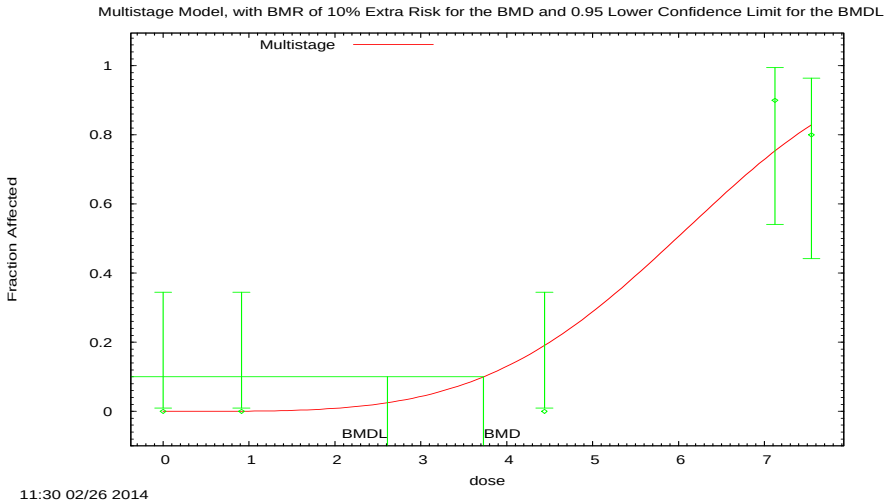
G: Multistage_f_resm_9_md4_NCMst2-BMR10



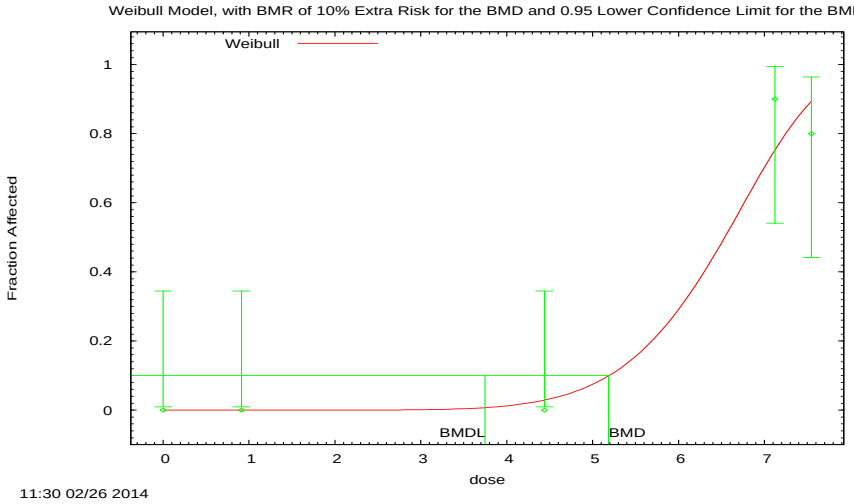
H: Multistage_f_resm_9_md4_NCMst3-BMR10



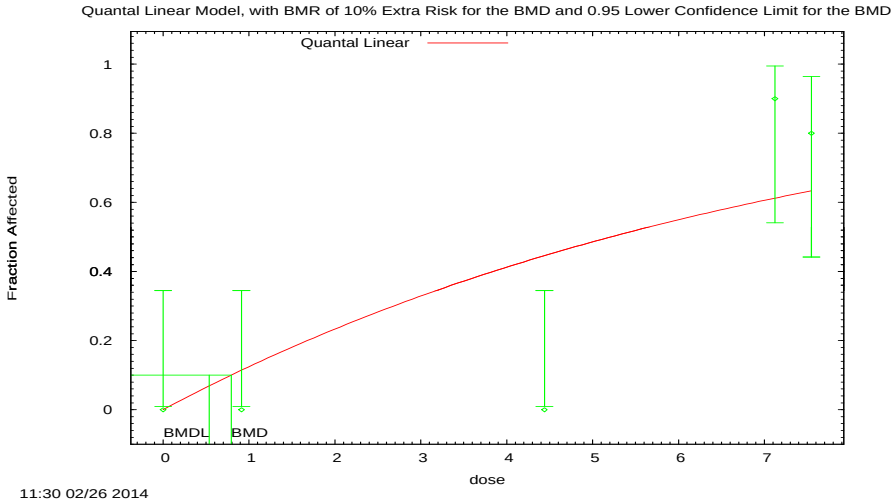
I: Multistage_f_resm_9_md4_NCMst4-BMR10



J: Weibull_f_resm_9_md4_Wei-BMR10



K: Quantal-Linear_f_resm_9_md4_Quant-BMR10



Quantitative Consideration of the Severity of Lesions Using Quantal BMDS Modeling Techniques

Male REH Lesions in the Subchronic (90-Day) Dodd et al. (2012) Study

Group	1	2	3	4	5
Amt Mtb (nmol/min-g)	**0**	**0.912448**	**4.438954**	**7.122926**	**7.547781**
Number Examined	10	10	10	10	10
With m_reh lesion*	0	0	10	10	10
Severity 1	0	0	10	6	6
Severity 2	0	0	0	4	4
Severity 3	0	0	0	0	0
Severity 4	0	0	0	0	0
Severity 5	0	0	0	0	0
Average Severity	--	--	1.00	1.40	1.40

m_reh_9 _md4

Group	Conc (ppm)	Amt Mtb (nmol/min-g)	N	Effect 1	Effect 2
1	0	0.000	10	0	0
2	0.1	0.912	10	0	0
3	1	4.439	10	10	0
4	10	7.123	10	10	4
5	30	7.548	10	10	4

BMD_{10}	2.00	5.84
$BMDL_{10}$	0.78	3.80

Dodd et al. Scale (1-5): 1= minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe, 5 = severe/high

**Level 2, Transitional respiratory epithelium hyperplasia*

Male RESM Lesions in the Subchronic (90-Day) Dodd et al. (2012) Study

Group	1	2	3	4	5
Amt Mtb (nmol/min-g)	**0**	**0.912448**	**4.438954**	**7.122926**	**7.547781**
Number Examined	10	10	10	10	10
With m_resm lesion*	0	0	0	8	8
Severity 1	0	0	0	7	8
Severity 2	0	0	0	1	0
Severity 3	0	0	0	0	0
Severity 4	0	0	0	0	0
Severity 5	0	0	0	0	0
Average Severity	--	--	--	0.90	0.80

m_resm_9 _md4

Group	Conc (ppm)	Amt Mtb (nmol/min-g)	N	Effect 1	Effect 2
1	0	0.000	10	0	0
2	0.1	0.912	10	0	0
3	1	4.439	10	0	0
4	10	7.123	10	8	1
5	30	7.548	10	8	0

BMD_{10}	5.12	--
$BMDL_{10}$	3.82	--

Dodd et al. Scale (1-5): 1= minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe, 5 = severe/high

**Level 2, Transitional respiratory epithelium squamous metaplasia*

Male OED Lesions in the Subchronic (90-Day) Dodd et al. (2012) Study

Group	1	2	3	4	5
Amt Mtb (nmol/min-g)	**0**	**0.141975**	**1.380519**	**10.21883**	**19.38274**
Number Examined	10	10	10	10	10
With m_oed lesion*	0	0	0	10	10
Severity 1	0	0	0	1	0
Severity 2	0	0	0	9	3
Severity 3	0	0	0	0	7
Severity 4	0	0	0	0	0
Severity 5	0	0	0	0	0
Average Severity	--	--	--	1.90	2.70

m_oed_9 _md4

Group	Conc (ppm)	Amt Mtb (nmol/min-g)	N	Effect 1	Effect 2
1	0	0.000	10	0	0
2	0.1	0.142	10	0	0
3	1	1.381	10	0	0
4	10	10.219	10	10	9
5	30	19.383	10	10	10

BMD_{10}	4.41	6.83
$BMDL_{10}$	1.25	1.60

Dodd et al. Scale (1-5): 1= minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe, 5 = severe/high

**Max severity of Levels 2-5, Olfactory epithelium degeneration*

Male OEH Lesions in the Subchronic (90-Day) Dodd et al. (2012) Study

Group	1	2	3	4	5
Amt Mtb (nmol/min-g)	**0**	**0.141975**	**1.380519**	**10.21883**	**19.38274**
Number Examined	10	10	10	10	10
With m_oeh lesion*	0	0	0	10	10
Severity 1	0	0	0	6	0
Severity 2	0	0	0	3	9
Severity 3	0	0	0	0	1
Severity 4	0	0	0	0	0
Severity 5	0	0	0	0	0
Average Severity	--	--	--	1.20	2.10

m_oeh_9 _md4

Group	Conc (ppm)	Amt Mtb (nmol/min-g)	N	Effect 1	Effect 2
1	0	0.000	10	0	0
2	0.1	0.142	10	0	0
3	1	1.381	10	0	0
4	10	10.219	10	9	3
5	30	19.383	10	10	10

BMD_{10}	6.83	8.84
$BMDL_{10}$	1.60	5.04

Dodd et al. Scale (1-5): 1= minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe, 5 = severe/high

**Max severity of Levels 2-5, Olfactory epithelium hyperplasia*

Notes:

Effect 1 = Incidence of all lesions

Effect 2 = Incidence of lesions having a severity $\geq$ 2.

BMDs = Average BMD (or BMDL) in nmol/min-g tissue

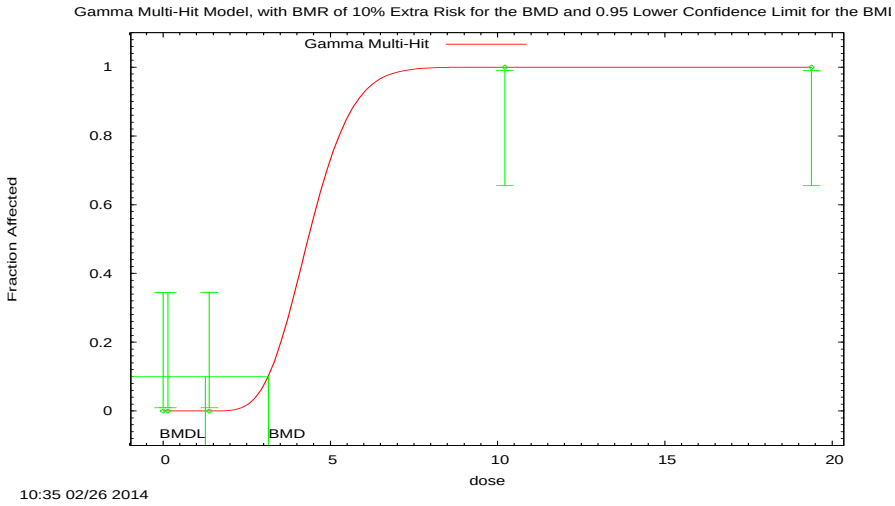
Model Name	Data File Name	Option File Name	AIC	Inputs + Estimates + Scaled Res.	P-value	Specified Effect	Risk Type	BMD	BMDL (POD)	Scaled residual for dose group near BMD	Δ BMD	Δ BMD:POD	Consider Model	POD selected	Selected POD	Average BMD	Average POD	POD Range	N	Model Note
Gamma	m_oed_9_md4.dax	Gam-BMR10.opt	2.00077	Array	1	0.1	Extra risk	3.14545	1.25963	-0.016	1.88582	1.497122	Y	N	--	--	--	--	--	
Logistic	m_oed_9_md4.dax	Log-BMR10.opt	4	Array	1	0.1	Extra risk	5.46189	1.2495	0	4.21239	3.371261	Y	N	--	--	--	--	--	
LogLogistic	m_oed_9_md4.dax	LogLog-BMR10.opt	2	Array	1	0.1	Extra risk	3.36446	1.29844	0	2.06602	1.591156	Y	Y	1.29844	4.4050143	1.24518857	0.20682	7	Selected over Weibull because of smaller delta BMD
Probit	m_oed_9_md4.dax	Probit-BMR10.opt	4	Array	1	0.1	Extra risk	5.26349	1.29435	0	3.96914	3.066512	Y	N	--	--	--	--	--	
LogProbit	m_oed_9_md4.dax	LogPro-BMR10.opt	4	Array	1	0.1	Extra risk	3.54958	1.29456	0	2.25502	1.74192	Y	N	--	--	--	--	--	
Multistage	m_oed_9_md4.dax	NCMst1-BMR10.opt	11.2155	Array	0.269	0.1	Extra risk	0.48343	0.279612	-0.561	0.203816	0.728924	N	N	--	--	--	--	--	Outlier AIC
Multistage	m_oed_9_md4.dax	NCMst2-BMR10.opt	3.84618	Array	0.9169	0.1	Extra risk	1.65623	0.823198	-0.872	0.833032	1.011946	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	m_oed_9_md4.dax	NCMst3-BMR10.opt	2.34613	Array	0.9964	0.1	Extra risk	2.65493	1.09162	-0.387	1.56331	1.432101	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Multistage	m_oed_9_md4.dax	NCMst4-BMR10.opt	2.0602	Array	0.9999	0.1	Extra risk	3.48114	0	-0.162	3.48114	#DIV/0!	N	N	--	--	--	--	--	BMDL = 0
Weibull	m_oed_9_md4.dax	Wei-BMR10.opt	2	Array	1	0.1	Extra risk	7.3953	1.22822	0	6.16708	5.021153	Y	N	--	--	--	--	--	
Quantal-Linear	m_oed_9_md4.dax	Quant-BMR10.opt	11.2155	Array	0.269	0.1	Extra risk	0.48343	0.279612	-0.561	0.203817	0.728928	N	N	--	--	--	--	--	Outlier AIC
Gamma	m_oed_9_sev_md4.dax	Gam-BMR10.opt	8.5017	Array	1	0.1	Extra risk	5.55041	1.22934	0	4.32107	3.514951	Y	N	--	--	--	--	--	
Logistic	m_oed_9_sev_md4.dax	Log-BMR10.opt	10.5017	Array	1	0.1	Extra risk	8.46206	2.61077	0	5.85129	2.241212	Y	N	--	--	--	--	--	
LogLogistic	m_oed_9_sev_md4.dax	LogLog-BMR10.opt	8.50168	Array	1	0.1	Extra risk	8.00536	1.34107	0	6.66429	4.969383	Y	Y	1.34107	6.8309243	1.60080429	1.43002	7	
Probit	m_oed_9_sev_md4.dax	Probit-BMR10.opt	10.5017	Array	1	0.1	Extra risk	7.03108	2.32816	0	4.70292	2.020016	Y	N	--	--	--	--	--	
LogProbit	m_oed_9_sev_md4.dax	LogPro-BMR10.opt	10.5017	Array	1	0.1	Extra risk	7.1478	1.30697	0	5.84083	4.468986	Y	N	--	--	--	--	--	
Multistage	m_oed_9_sev_md4.dax	NCMst1-BMR10.opt	14.8856	Array	0.4541	0.1	Extra risk	0.60426	0.369705	-0.501	0.234553	0.634433	N	N	--	--	--	--	--	Outlier AIC
Multistage	m_oed_9_sev_md4.dax	NCMst2-BMR10.opt	9.33136	Array	0.9797	0.1	Extra risk	2.25548	0.947395	-0.635	1.308085	1.380718	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	m_oed_9_sev_md4.dax	NCMst3-BMR10.opt	8.6149	Array	0.9996	0.1	Extra risk	3.66674	1.14535	-0.238	2.52139	2.201414	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	m_oed_9_sev_md4.dax	NCMst4-BMR10.opt	8.51701	Array	1	0.1	Extra risk	4.72787	1.18075	-0.088	3.54712	3.004124	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Weibull	m_oed_9_sev_md4.dax	Wei-BMR10.opt	10.5017	Array	1	0.1	Extra risk	6.89189	1.20857	0	5.68332	4.702516	Y	N	--	--	--	--	--	
Quantal-Linear	m_oed_9_sev_md4.dax	Quant-BMR10.opt	14.8856	Array	0.4541	0.1	Extra risk	0.60425	0.369704	-0.501	0.23455	0.634426	N	N	--	--	--	--	--	Outlier AIC
Gamma	m_oeh_9_md4.dax	Gam-BMR10.opt	8.5017	Array	1	0.1	Extra risk	5.55041	1.22934	0	4.32107	3.514951	Y	N	--	--	--	--	--	
Logistic	m_oeh_9_md4.dax	Log-BMR10.opt	10.5017	Array	1	0.1	Extra risk	8.46206	2.61077	0	5.85129	2.241212	Y	N	--	--	--	--	--	
LogLogistic	m_oeh_9_md4.dax	LogLog-BMR10.opt	8.50168	Array	1	0.1	Extra risk	8.00536	1.34107	0	6.66429	4.969383	Y	Y	1.34107	6.8309243	1.60080429	1.43002	7	
Probit	m_oeh_9_md4.dax	Probit-BMR10.opt	10.5017	Array	1	0.1	Extra risk	7.03108	2.32816	0	4.70292	2.020016	Y	N	--	--	--	--	--	
LogProbit	m_oeh_9_md4.dax	LogPro-BMR10.opt	10.5017	Array	1	0.1	Extra risk	7.1478	1.30697	0	5.84083	4.468986	Y	N	--	--	--	--	--	
Multistage	m_oeh_9_md4.dax	NCMst1-BMR10.opt	14.8856	Array	0.4541	0.1	Extra risk	0.60426	0.369705	-0.501	0.234553	0.634433	N	N	--	--	--	--	--	Outlier AIC
Multistage	m_oeh_9_md4.dax	NCMst2-BMR10.opt	9.33136	Array	0.9797	0.1	Extra risk	2.25548	0.947395	-0.635	1.308085	1.380718	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	m_oeh_9_md4.dax	NCMst3-BMR10.opt	8.6149	Array	0.9996	0.1	Extra risk	3.66674	1.14535	-0.238	2.52139	2.201414	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	m_oeh_9_md4.dax	NCMst4-BMR10.opt	8.51701	Array	1	0.1	Extra risk	4.72787	1.18075	-0.088	3.54712	3.004124	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Weibull	m_oeh_9_md4.dax	Wei-BMR10.opt	10.5017	Array	1	0.1	Extra risk	6.89189	1.20857	0	5.68332	4.702516	Y	N	--	--	--	--	--	

Model Name	Data File Name	Option File Name	AIC	Inputs + Estimates + Scaled Res.	P-value	Specified Effect	Risk Type	BMD	BMDL (POD)	Scaled residual for dose group near BMD	Δ BMD	Δ BMD:POD	Consider Model	POD selected	Selected POD	Average BMD	Average POD	POD Range	N	Model Note
Quantal-Linear	m_oeh_9_md4.dax	Quant-BMR10.opt	14.8856	Array	0.4541	0.1	Extra risk	0.60425	0.369704	-0.501	0.23455	0.634426	N	N	--	--	--	--	--	Outlier AIC
Gamma	m_oeh_9_sev_md4.dax	Gam-BMR10.opt	14.3863	Array	0.999	0.1	Extra risk	8.32568	5.33106	-0.111	2.99462	0.561731	Y	N	--	--	--	--	--	
Logistic	m_oeh_9_sev_md4.dax	Log-BMR10.opt	16.2173	Array	1	0.1	Extra risk	9.60576	5.47701	0	4.12875	0.753833	Y	N	--	--	--	--	--	
LogLogistic	m_oeh_9_sev_md4.dax	LogLog-BMR10.opt	14.2177	Array	1	0.1	Extra risk	9.48059	6.21293	0	3.26766	0.525945	Y	Y	6.21293	8.84077	5.04054714	3.56279	7	
Probit	m_oeh_9_sev_md4.dax	Probit-BMR10.opt	16.2173	Array	1	0.1	Extra risk	9.09481	4.89411	0	4.2007	0.858317	Y	N	--	--	--	--	--	
LogProbit	m_oeh_9_sev_md4.dax	LogPro-BMR10.opt	16.2173	Array	1	0.1	Extra risk	9.44871	6.15695	0	3.29176	0.534641	Y	N	--	--	--	--	--	
Multistage	m_oeh_9_sev_md4.dax	NCMst1-BMR10.opt	24.0867	Array	0.1674	0.1	Extra risk	1.41452	0.890032	-1.041	0.524488	0.589291	N	N	--	--	--	--	--	Outlier AIC
Multistage	m_oeh_9_sev_md4.dax	NCMst2-BMR10.opt	17.7981	Array	0.654	0.1	Extra risk	4.12365	2.19006	-0.345	1.93359	0.882894	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	m_oeh_9_sev_md4.dax	NCMst3-BMR10.opt	15.2917	Array	0.9496	0.1	Extra risk	6.09156	2.81387	-0.595	3.27769	1.164833	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	m_oeh_9_sev_md4.dax	NCMst4-BMR10.opt	14.3726	Array	0.999	0.1	Extra risk	7.34804	2.65014	-0.174	4.6979	1.772699	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Weibull	m_oeh_9_sev_md4.dax	Wei-BMR10.opt	16.2173	Array	1	0.1	Extra risk	8.5818	4.56163	0	4.02017	0.881301	Y	N	--	--	--	--	--	
Quantal-Linear	m_oeh_9_sev_md4.dax	Quant-BMR10.opt	24.0867	Array	0.1674	0.1	Extra risk	1.41452	0.890032	-1.041	0.524488	0.589291	N	N	--	--	--	--	--	Outlier AIC
Gamma	m_reh_9_md4.dax	Gam-BMR10.opt	2.02031	Array	1	0.1	Extra risk	1.58754	0.850208	-0.08	0.737332	0.867237	Y	N	--	--	--	--	--	
Logistic	m_reh_9_md4.dax	Log-BMR10.opt	4	Array	1	0.1	Extra risk	2.65507		0	2.65507	#DIV/0!	N	N	--	--	--	--	--	Benchmark dose computation failed. Lower limit includes zero.
LogLogistic	m_reh_9_md4.dax	LogLog-BMR10.opt	2.00003	Array	1	0.1	Extra risk	1.78083	0.868999	-0.003	0.911831	1.049289	Y	N	--	--	--	--	--	
Probit	m_reh_9_md4.dax	Probit-BMR10.opt	4	Array	1	0.1	Extra risk	2.53256	0.848426	0	1.684134	1.98501	Y	N	--	--	--	--	--	
LogProbit	m_reh_9_md4.dax	LogPro-BMR10.opt	4	Array	1	0.1	Extra risk	2.34713		0	2.34713	#DIV/0!	N	N	--	--	--	--	--	Benchmark dose computation failed. Lower limit includes zero.
Multistage	m_reh_9_md4.dax	NCMst1-BMR10.opt	14.461	Array	0.1101	0.1	Extra risk	0.20961	0.133088	0	0.076521	0.574965	N	N	--	--	--	--	--	Outlier AIC
Multistage	m_reh_9_md4.dax	NCMst2-BMR10.opt	5.54066	Array	0.7586	0.1	Extra risk	0.8021	0.431569	-1.208	0.370534	0.858574	N	N	--	--	--	--	--	Outlier AIC
Multistage	m_reh_9_md4.dax	NCMst3-BMR10.opt	2.99764	Array	0.9727	0.1	Extra risk	1.24667	0.60842	-0.649	0.63825	1.049029	Y	N	--	--	--	--	--	
Multistage	m_reh_9_md4.dax	NCMst4-BMR10.opt	2.26124	Array	0.9979	0.1	Extra risk	1.59436	0.682118	-0.337	0.912242	1.337367	Y	N	--	--	--	--	--	
Weibull	m_reh_9_md4.dax	Wei-BMR10.opt	2	Array	1	0.1	Extra risk	3.2522	0.82734	0	2.42486	2.930911	Y	Y	0.82734	1.9990267	0.7809185	0.260579	6	
Quantal-Linear	m_reh_9_md4.dax	Quant-BMR10.opt	14.461	Array	0.1101	0.1	Extra risk	0.20961	0.133088	0	0.07652	0.574958	N	N	--	--	--	--	--	Outlier AIC
Gamma	m_reh_9_sev_md4.dax	Gam-BMR10.opt	29.3931	Array	0.9876	0.1	Extra risk	5.693	3.80194	-0.38	1.89106	0.497393	Y	Y	3.80194	5.8406729	3.80131	1.12032	7	
Logistic	m_reh_9_sev_md4.dax	Log-BMR10.opt	31.57	Array	0.907	0.1	Extra risk	6.09992	4.20686	0.52	1.89306	0.449994	Y	N	--	--	--	--	--	
LogLogistic	m_reh_9_sev_md4.dax	LogLog-BMR10.opt	31.3889	Array	0.94	0.1	Extra risk	6.02082	3.81058	0.439	2.21024	0.580027	Y	N	--	--	--	--	--	
Probit	m_reh_9_sev_md4.dax	Probit-BMR10.opt	31.379	Array	0.938	0.1	Extra risk	6.05205	4.06723	0.459	1.98482	0.488003	Y	N	--	--	--	--	--	
LogProbit	m_reh_9_sev_md4.dax	LogPro-BMR10.opt	31.2369	Array	0.9628	0.1	Extra risk	5.95058	3.93067	0.379	2.01991	0.513884	Y	N	--	--	--	--	--	
Multistage	m_reh_9_sev_md4.dax	NCMst1-BMR10.opt	35.0278	Array	0.4214	0.1	Extra risk	2.22816	1.30659	-0.664	0.92157	0.705325	N	N	--	--	--	--	--	Outlier AIC
Multistage	m_reh_9_sev_md4.dax	NCMst2-BMR10.opt	32.427	Array	0.7217	0.1	Extra risk	3.72282	1.93396	-1.271	1.78886	0.924973	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	m_reh_9_sev_md4.dax	NCMst3-BMR10.opt	31.1068	Array	0.8703	0.1	Extra risk	4.53793	2.62544	-1.018	1.91249	0.728446	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	m_reh_9_sev_md4.dax	NCMst4-BMR10.opt	30.3351	Array	0.937	0.1	Extra risk	5.05377	3.08654	-0.804	1.96723	0.637358	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Weibull	m_reh_9_sev_md4.dax	Wei-BMR10.opt	31.5149	Array	0.9182	0.1	Extra risk	6.01457	3.70535	0.507	2.30922	0.623212	Y	N	--	--	--	--	--	

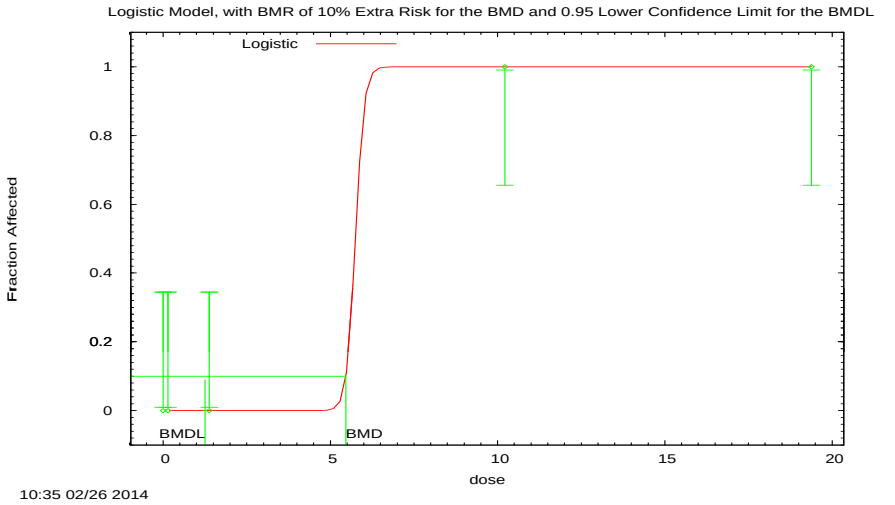
Model Name	Data File Name	Option File Name	AIC	Inputs + Estimates + Scaled Res.	P-value	Specified Effect	Risk Type	BMD	BMDL (POD)	Scaled residual for dose group near BMD	Δ BMD	Δ BMD:POD	Consider Model	POD selected	Selected POD	Average BMD	Average POD	POD Range	N	Model Note
Quantal-Linear	m_reh_9_sev_md4.dax	Quant-BMR10.opt	35.0278	Array	0.4214	0.1	Extra risk	2.22816	1.30659	-0.664	0.92157	0.705325	N	N	--	--	--	--	--	Outlier AIC
Gamma	m_resm_9_md4.dax	Gam-BMR10.opt	24.2219	Array	0.8597	0.1	Extra risk	4.52949	3.73717	-0.978	0.79232	0.212011	Y	Y	3.73717	5.11611	3.81894571	1.51488	7	
Logistic	m_resm_9_md4.dax	Log-BMR10.opt	24.8318	Array	0.8654	0.1	Extra risk	5.59068	4.02387	-0.32	1.56681	0.389379	Y	N	--	--	--	--	--	
LogLogistic	m_resm_9_md4.dax	LogLog-BMR10.opt	24.5845	Array	0.9165	0.1	Extra risk	5.52695	4.13921	-0.261	1.38774	0.335267	Y	N	--	--	--	--	--	
Probit	m_resm_9_md4.dax	Probit-BMR10.opt	24.729	Array	0.8825	0.1	Extra risk	5.49706	4.06654	-0.25	1.43052	0.351778	Y	N	--	--	--	--	--	
LogProbit	m_resm_9_md4.dax	LogPro-BMR10.opt	24.4946	Array	0.9309	0.1	Extra risk	5.41249	4.19841	-0.196	1.21408	0.289176	Y	N	--	--	--	--	--	
Multistage	m_resm_9_md4.dax	NCMst1-BMR10.opt	39.0358	Array	0.0174	0.1	Extra risk	0.87587	0.58688	-1.077	0.288987	0.492412	N	N	--	--	--	--	--	P-value too low
Multistage	m_resm_9_md4.dax	NCMst2-BMR10.opt	32.188	Array	0.1503	0.1	Extra risk	2.25608	1.43287	-0.417	0.82321	0.574518	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	m_resm_9_md4.dax	NCMst3-BMR10.opt	28.478	Array	0.4058	0.1	Extra risk	3.19915	2.15545	-1.803	1.0437	0.484214	N	N	--	--	--	--	--	Not selected as Multistage because another has better fit
Multistage	m_resm_9_md4.dax	NCMst4-BMR10.opt	26.1855	Array	0.6511	0.1	Extra risk	3.85471	2.68353	-1.427	1.17118	0.436433	Y	N	--	--	--	--	--	Selected as Multistage because has smallest AIC and largest P value
Weibull	m_resm_9_md4.dax	Wei-BMR10.opt	25.232	Array	0.7931	0.1	Extra risk	5.40139	3.88389	-0.435	1.5175	0.390717	Y	N	--	--	--	--	--	
Quantal-Linear	m_resm_9_md4.dax	Quant-BMR10.opt	39.0358	Array	0.0174	0.1	Extra risk	0.87587	0.58688	-1.077	0.288987	0.492412	N	N	--	--	--	--	--	P-value too low
Gamma	m_resm_9_sev_md4.dax	Gam-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Logistic	m_resm_9_sev_md4.dax	Log-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
LogLogistic	m_resm_9_sev_md4.dax	LogLog-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Probit	m_resm_9_sev_md4.dax	Probit-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
LogProbit	m_resm_9_sev_md4.dax	LogPro-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Multistage	m_resm_9_sev_md4.dax	NCMst1-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Multistage	m_resm_9_sev_md4.dax	NCMst2-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Multistage	m_resm_9_sev_md4.dax	NCMst3-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Multistage	m_resm_9_sev_md4.dax	NCMst4-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Weibull	m_resm_9_sev_md4.dax	Wei-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS
Quantal-Linear	m_resm_9_sev_md4.dax	Quant-BMR10.opt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Could not run in BMDS

Model excluded from average
Reason for model exclusion
Selected model (best fit)

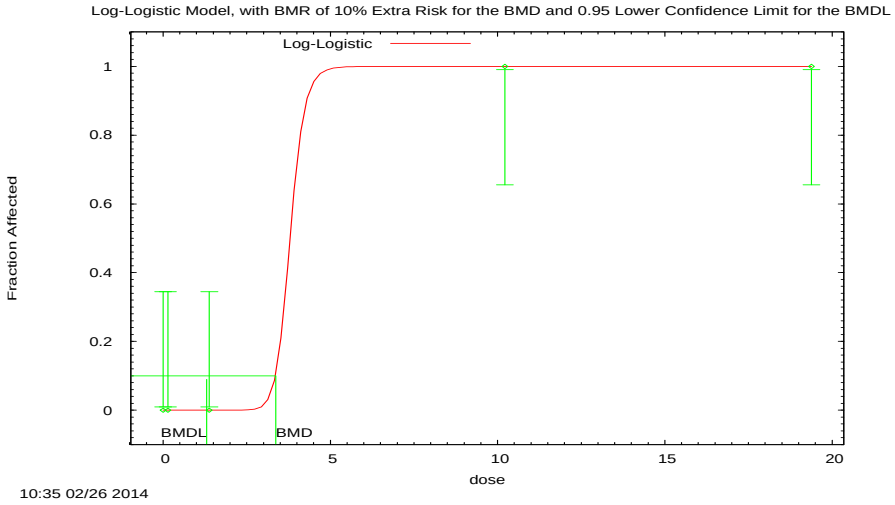
A: Gamma_m_oed_9_md4_Gam-BMR10



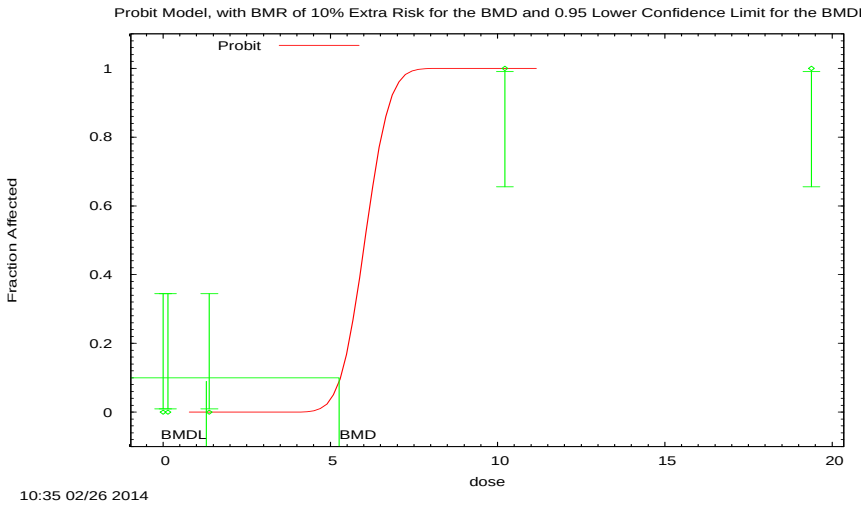
B: Logistic_m_oed_9_md4_Log-BMR10



C: LogLogistic_m_oed_9_md4_LogLog-BMR10



D: Probit_m_oed_9_md4_Probit-BMR10



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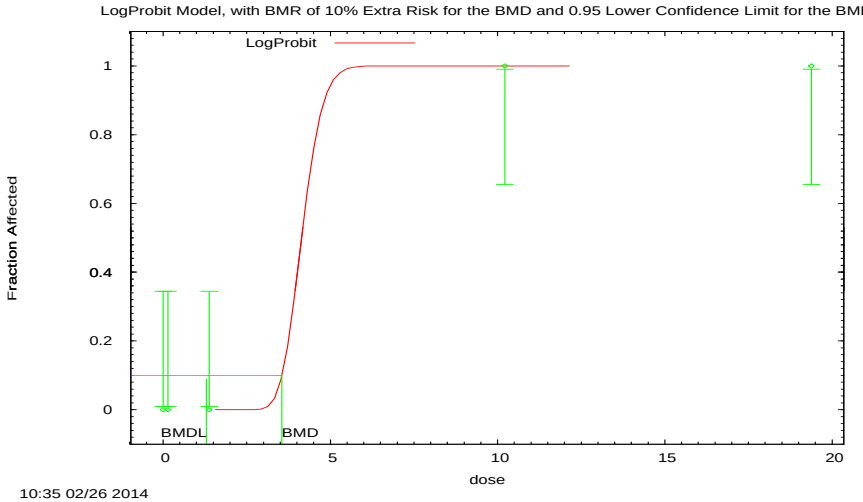
E: LogProbit_m_oed_9_md4_LogPro-BMR10



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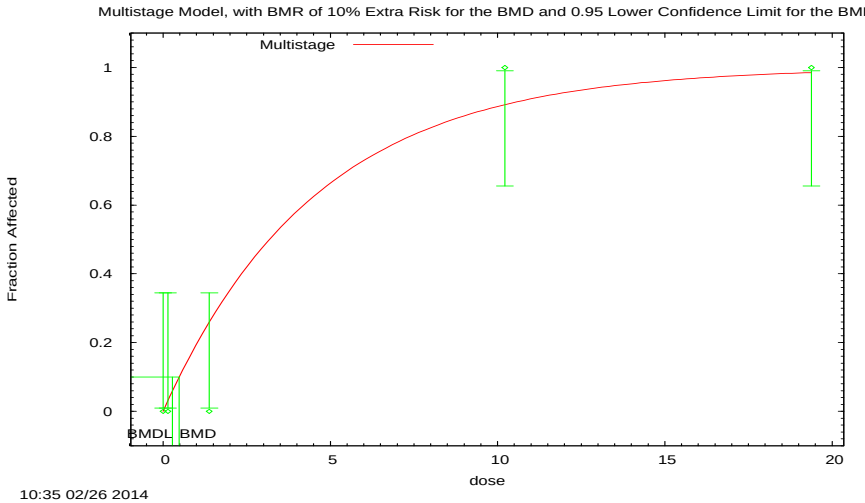
F: Multistage_m_oed_9_md4_NCMst1-BMR10



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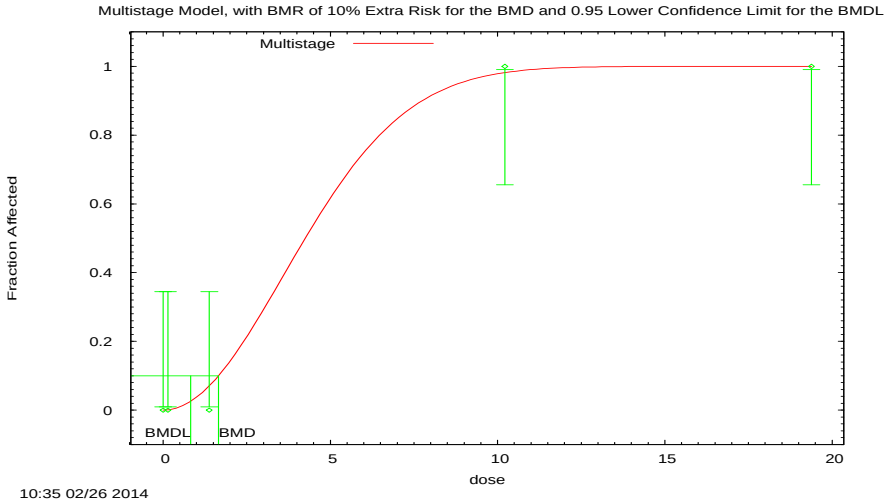
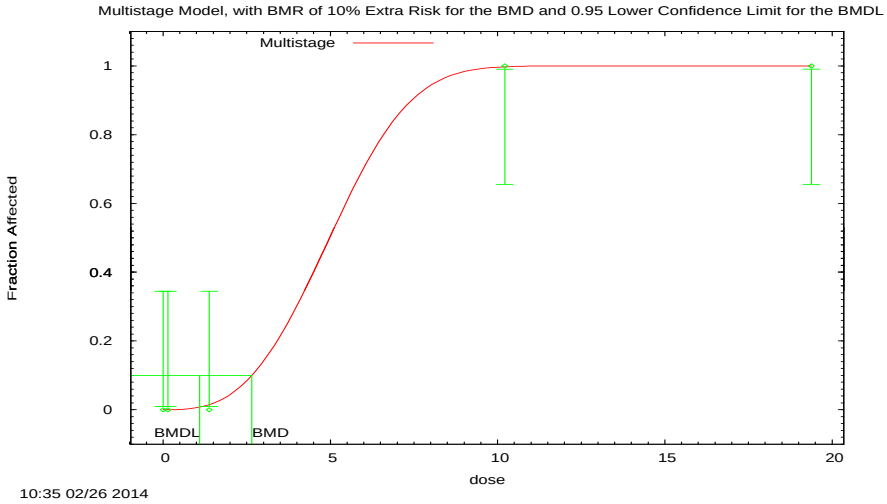
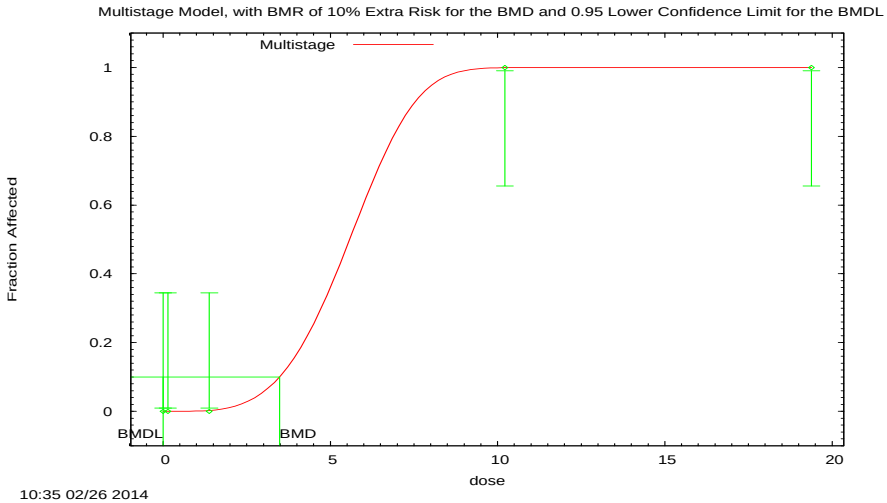
G: Multistage_m_oed_9_md4_NCMst2-BMR10



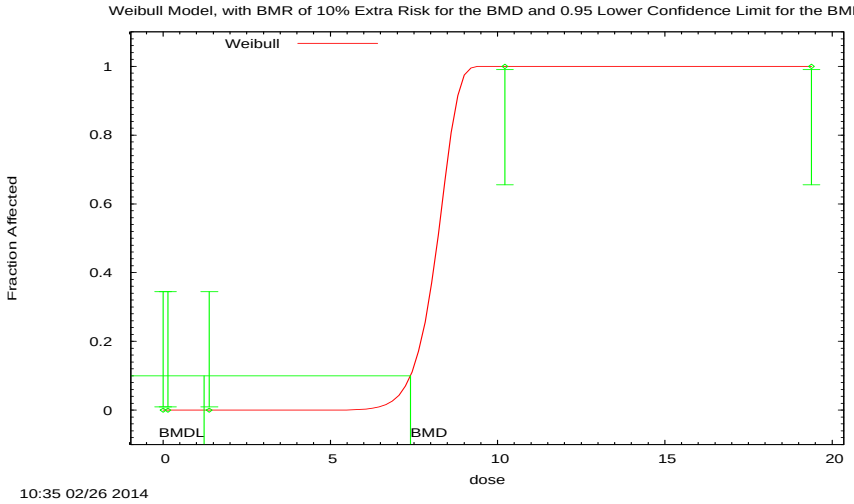
H: Multistage_m_oed_9_md4_NCMst3-BMR10



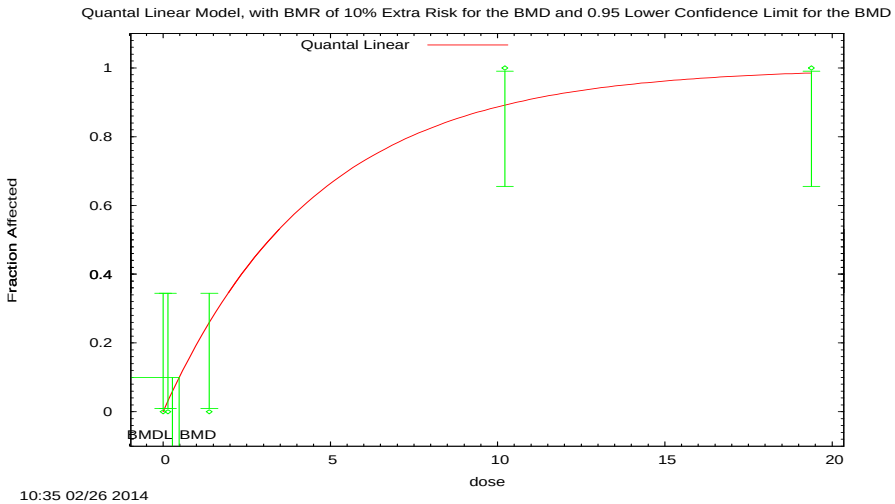
I: Multistage_m_oed_9_md4_NCMst4-BMR10



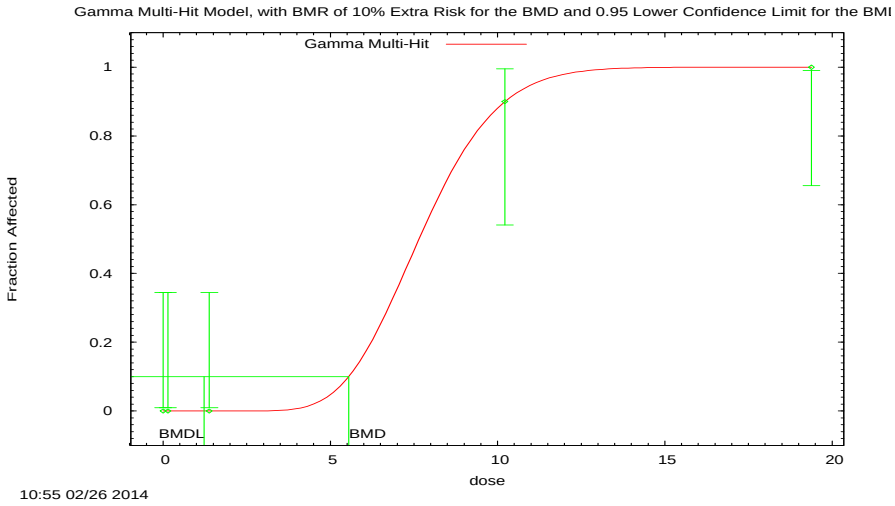
J: Weibull_m_oed_9_md4_Wei-BMR10



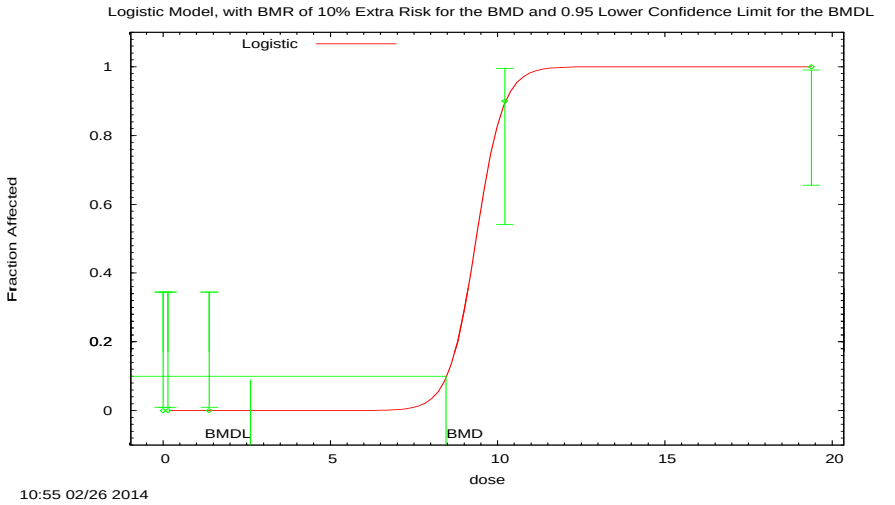
K: Quantal-Linear_m_oed_9_md4_Quant-BMR10



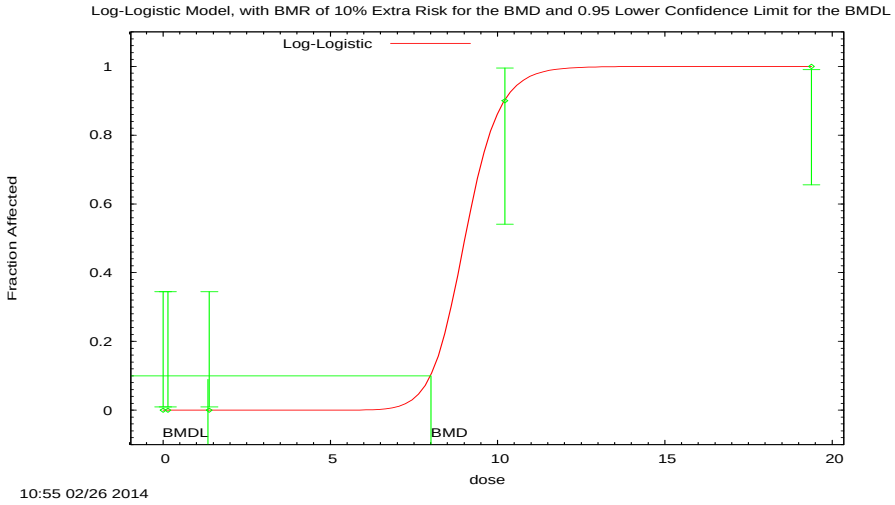
A: Gamma_m_oeh_9_md4_Gam-BMR10



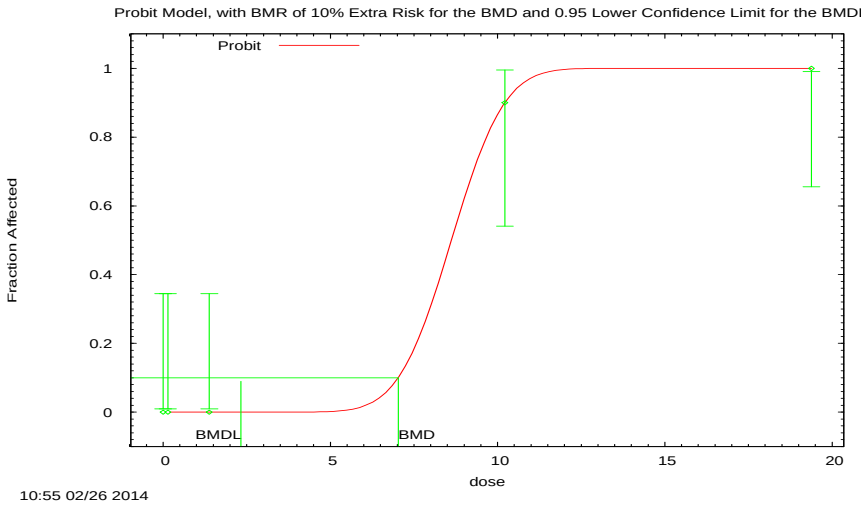
B: Logistic_m_oeh_9_md4_Log-BMR10



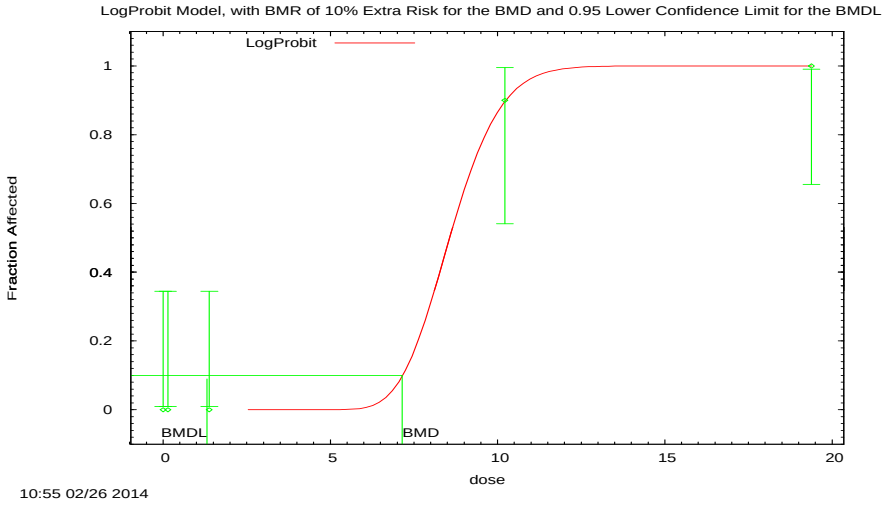
C: LogLogistic_m_oeh_9_md4_LogLog-BMR10



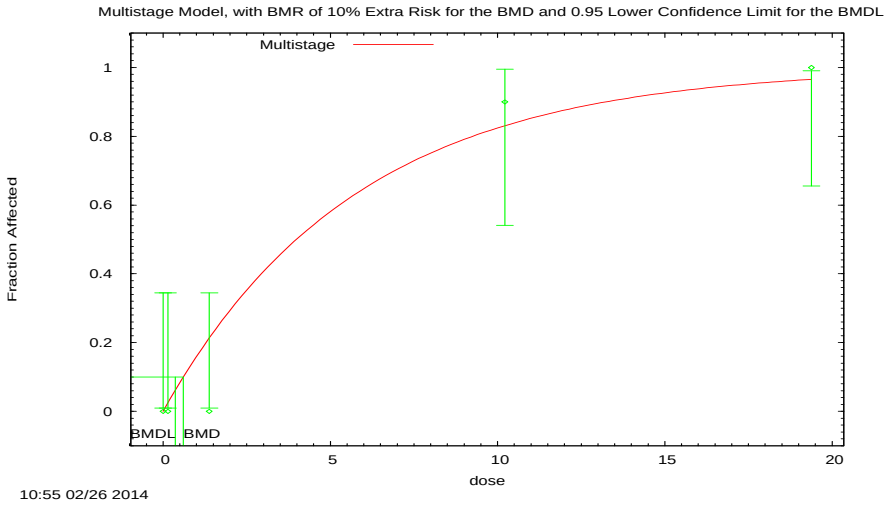
D: Probit_m_oeh_9_md4_Probit-BMR10



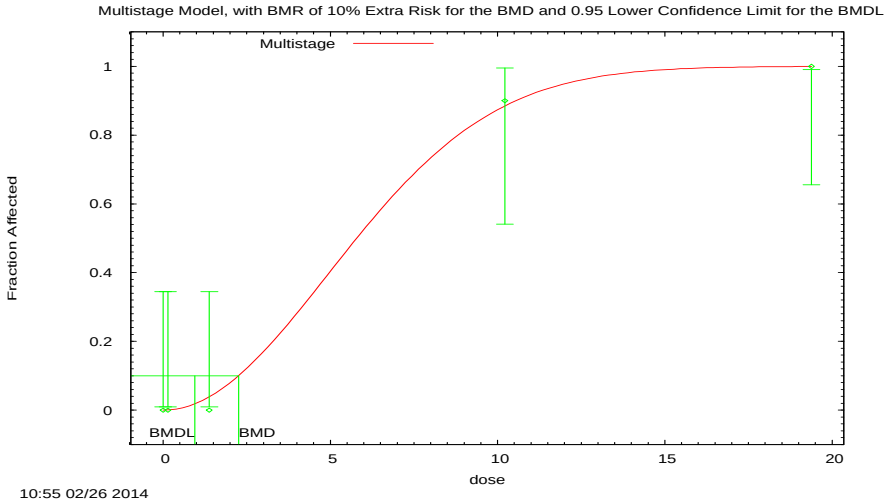
E: LogProbit_m_oeh_9_md4_LogPro-BMR10



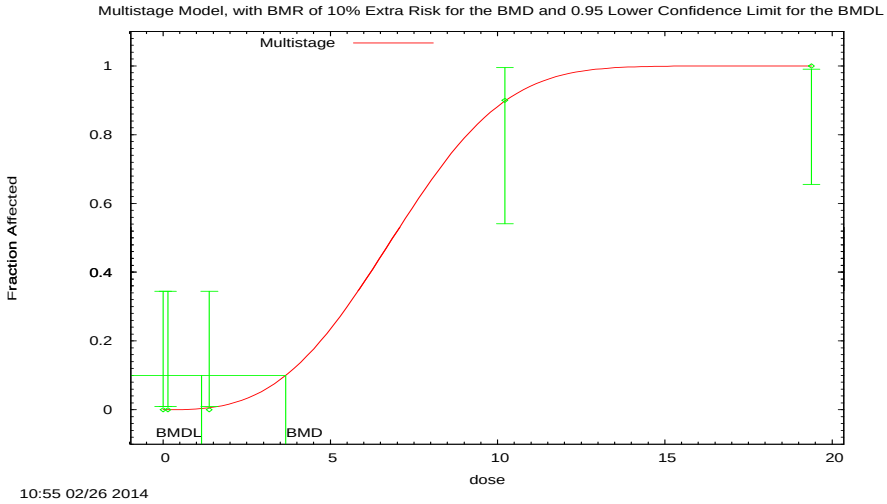
F: Multistage_m_oeh_9_md4_NCMst1-BMR10



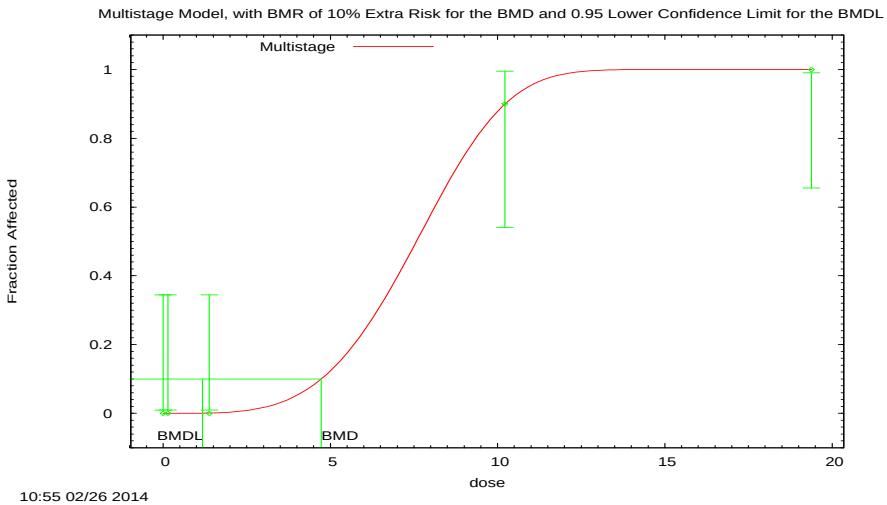
G: Multistage_m_oeh_9_md4_NCMst2-BMR10



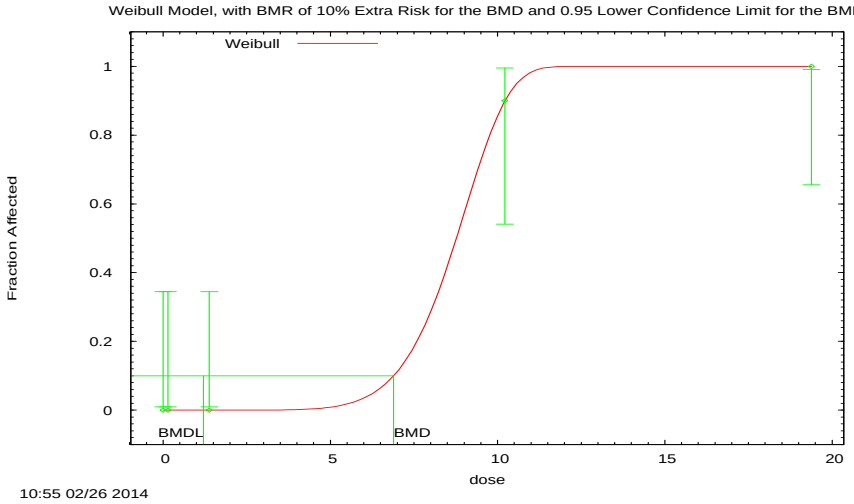
H: Multistage_m_oeh_9_md4_NCMst3-BMR10



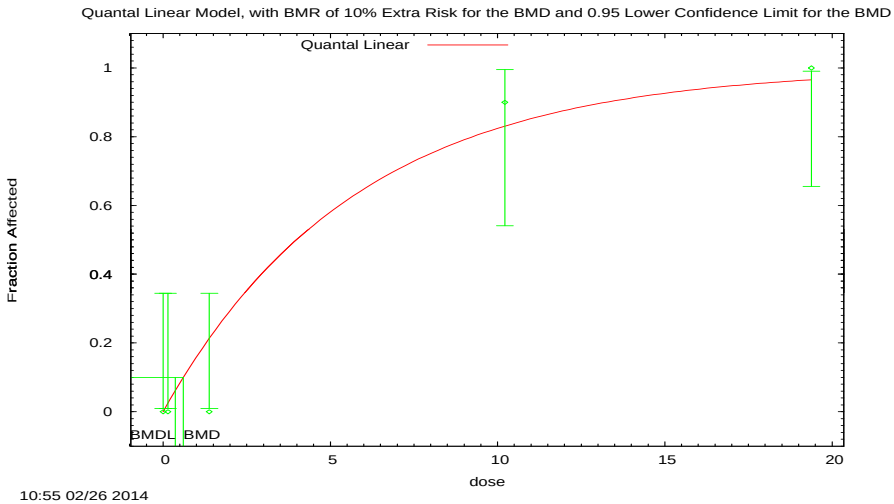
I: Multistage_m_oeh_9_md4_NCMst4-BMR10



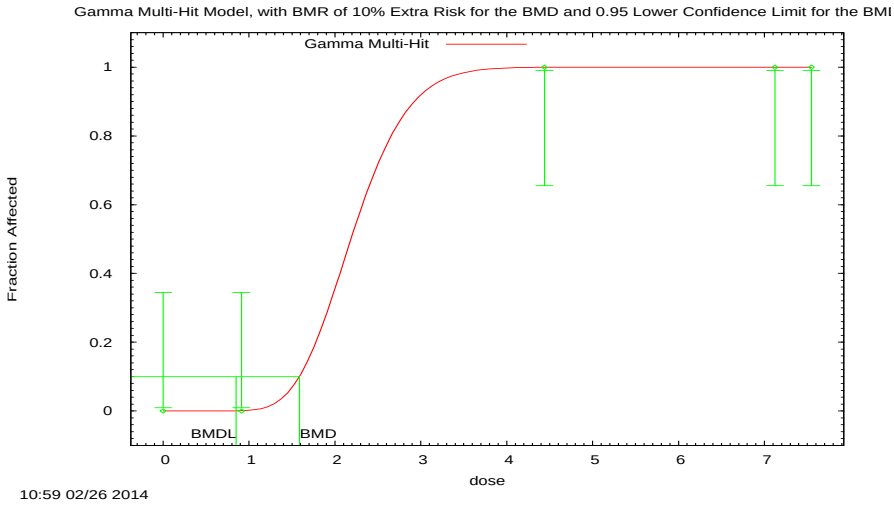
J: Weibull_m_oeh_9_md4_Wei-BMR10



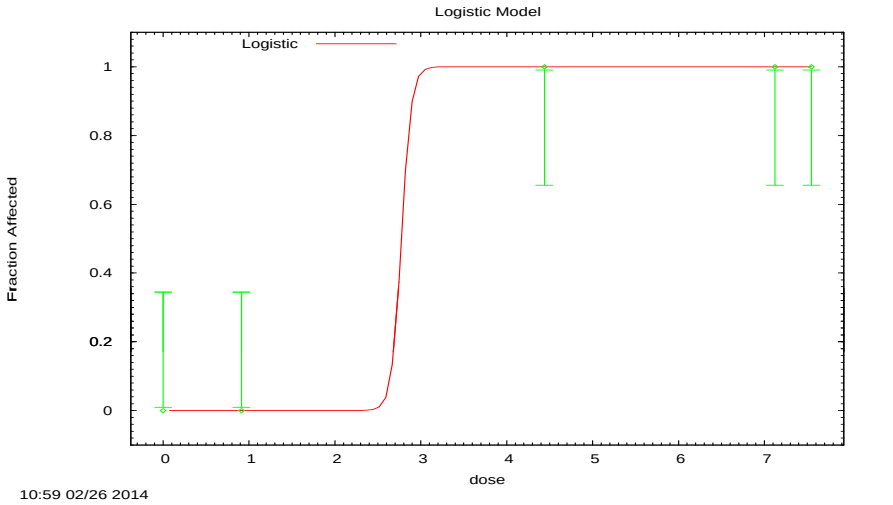
K: Quantal-Linear_m_oeh_9_md4_Quant-BMR10



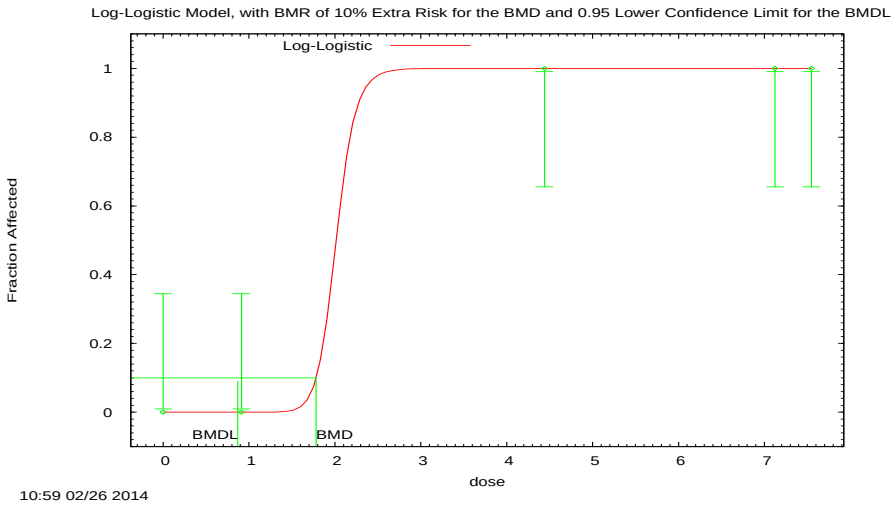
A: Gamma_m_reh_9_md4_Gam-BMR10



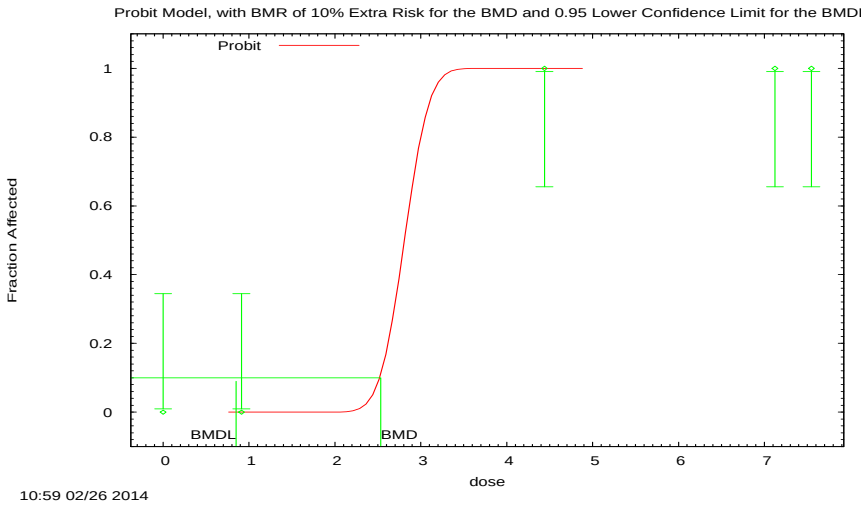
B: Logistic_m_reh_9_md4_Log-BMR10



C: LogLogistic_m_reh_9_md4_LogLog-BMR10



D: Probit_m_reh_9_md4_Probit-BMR10



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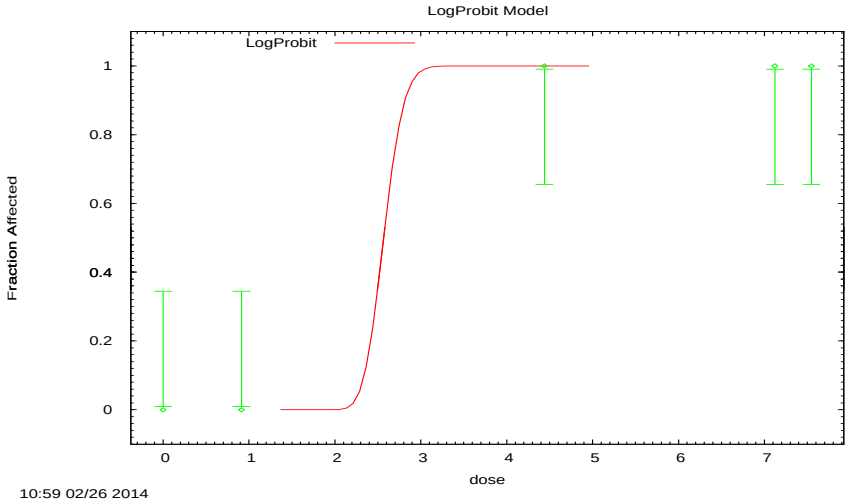
E: LogProbit_m_reh_9_md4_LogPro-BMR10



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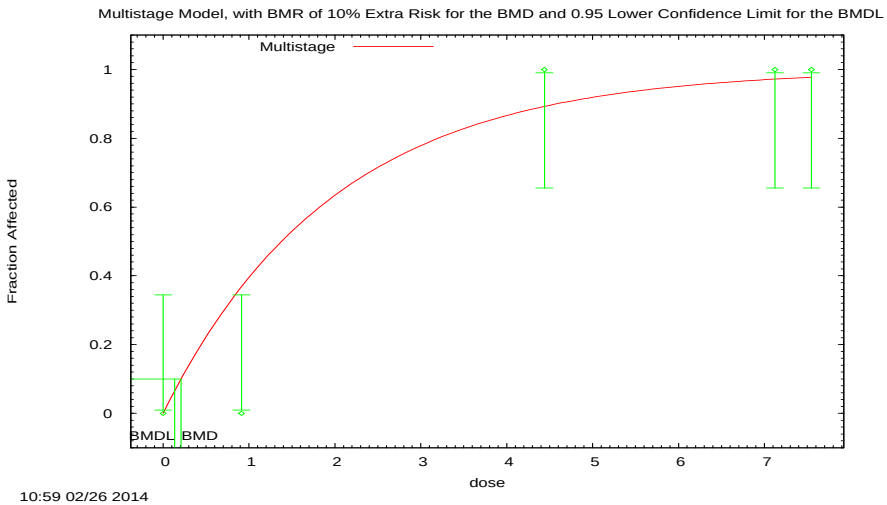
F: Multistage_m_reh_9_md4_NCMst1-BMR10



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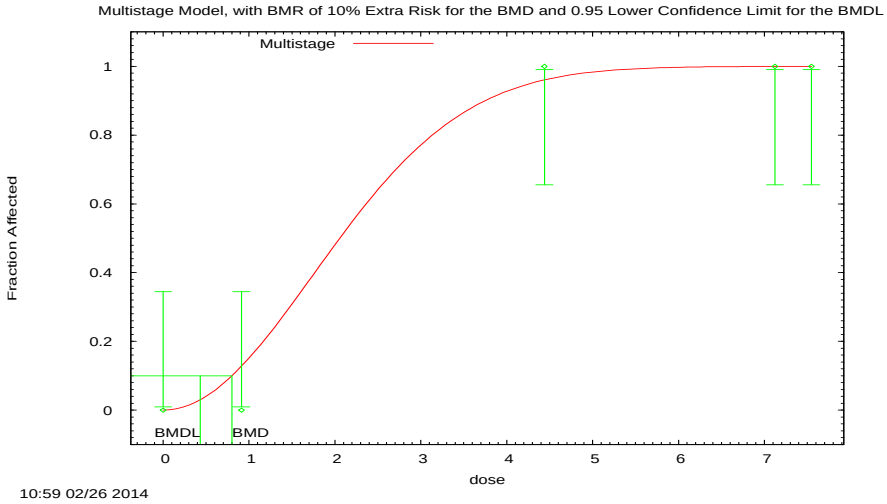
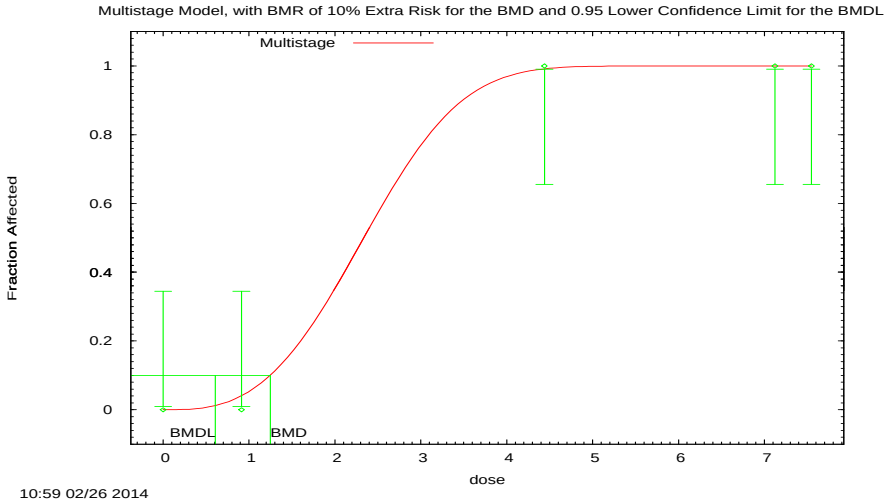
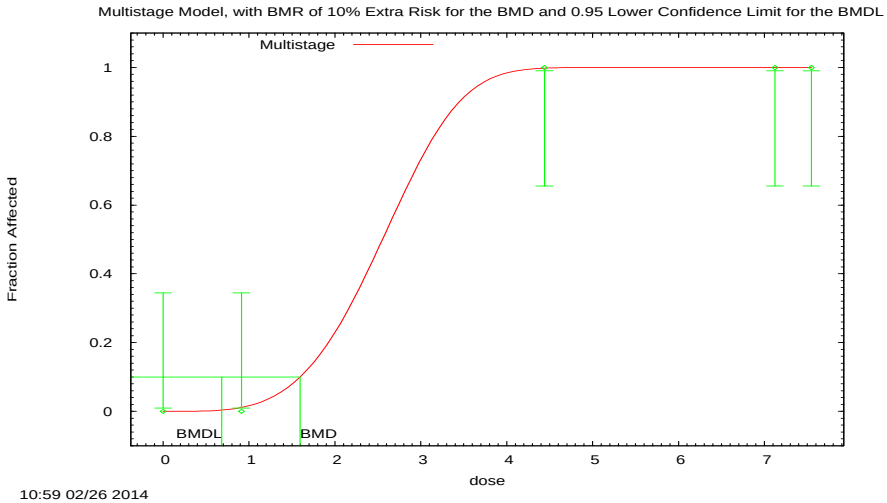
G: Multistage_m_reh_9_md4_NCMst2-BMR10



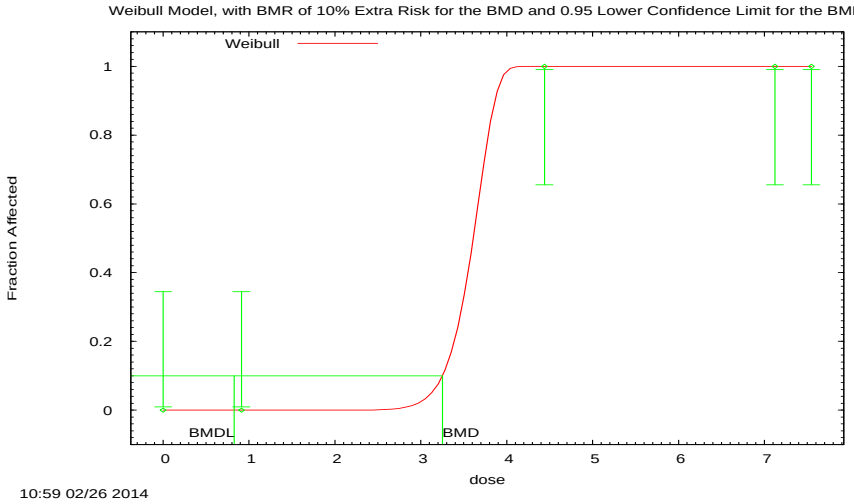
H: Multistage_m_reh_9_md4_NCMst3-BMR10



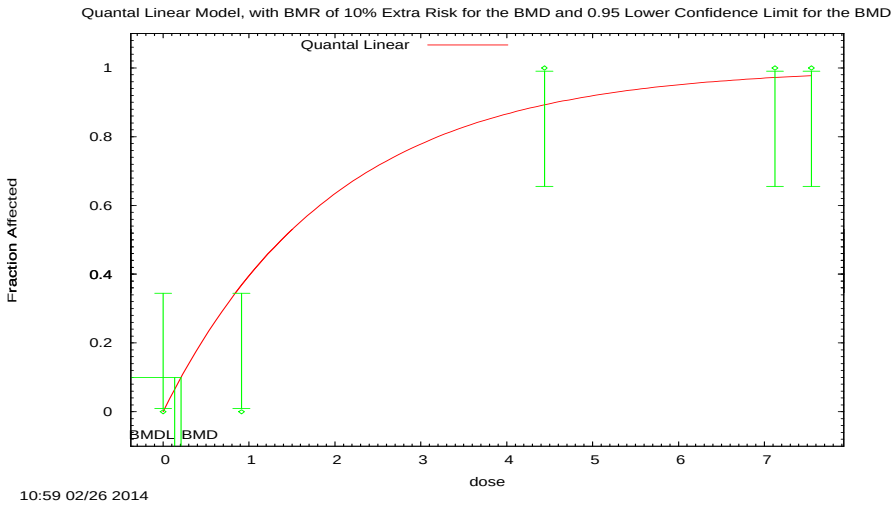
I: Multistage_m_reh_9_md4_NCMst4-BMR10



J: Weibull_m_reh_9_md4_Wei-BMR10



K: Quantal-Linear_m_reh_9_md4_Quant-BMR10



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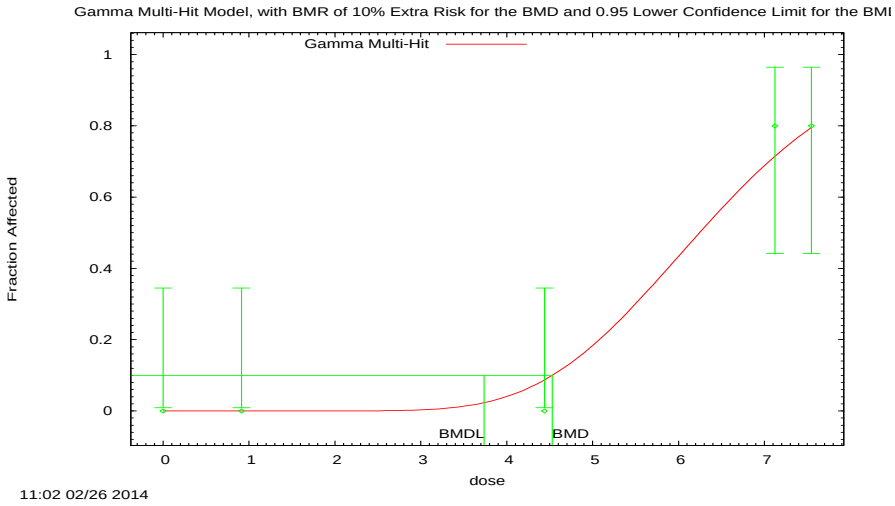

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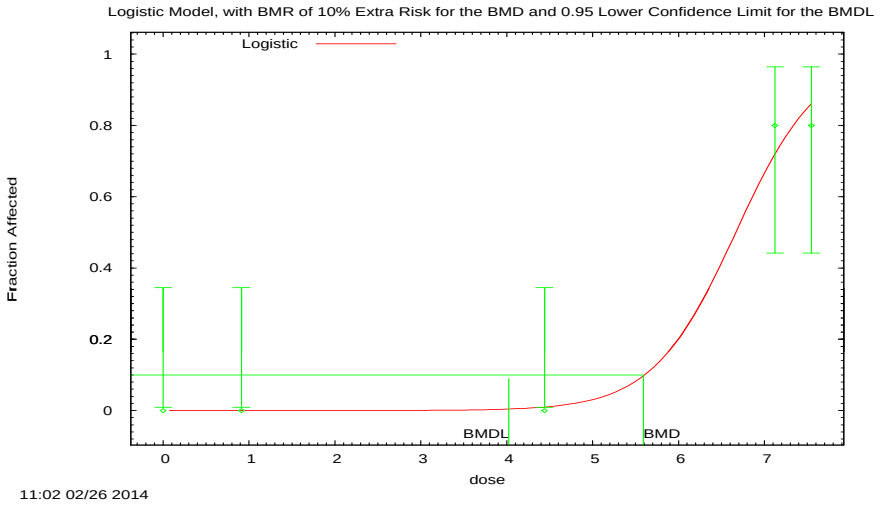

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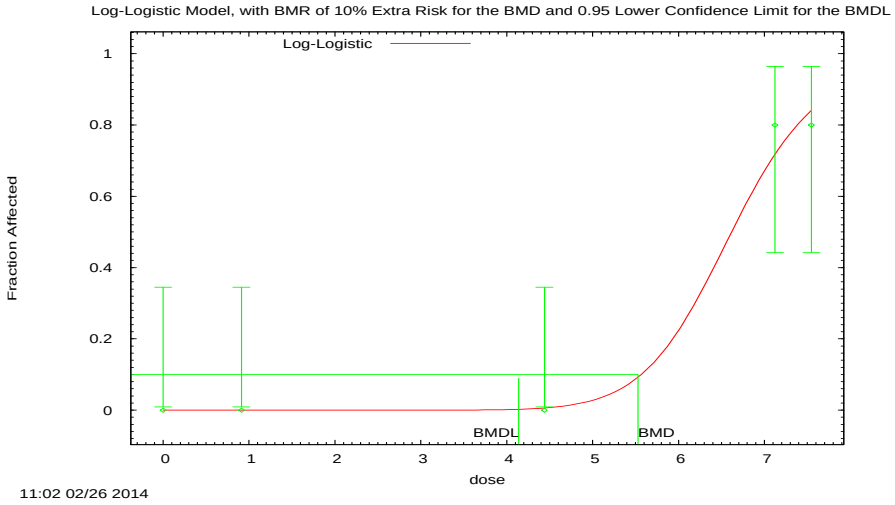

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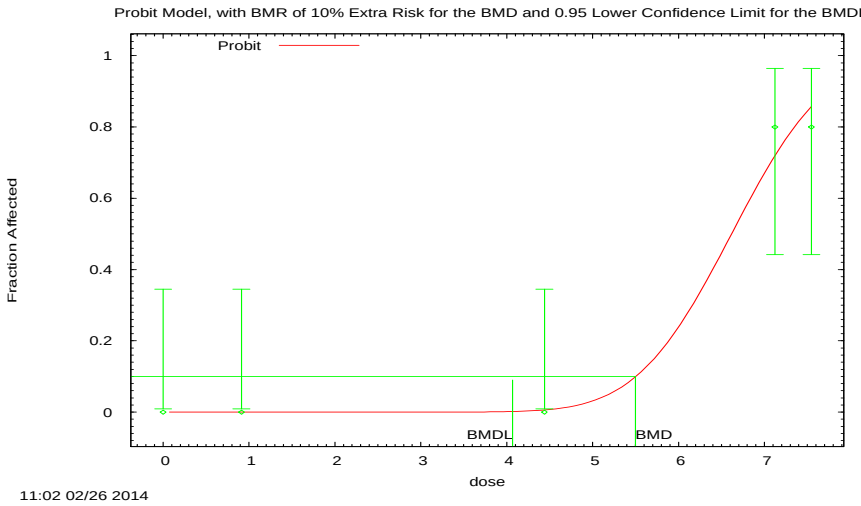

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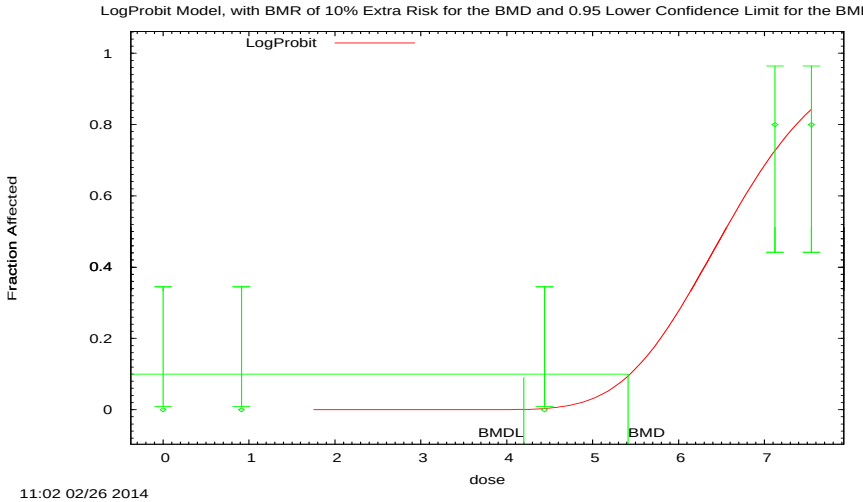

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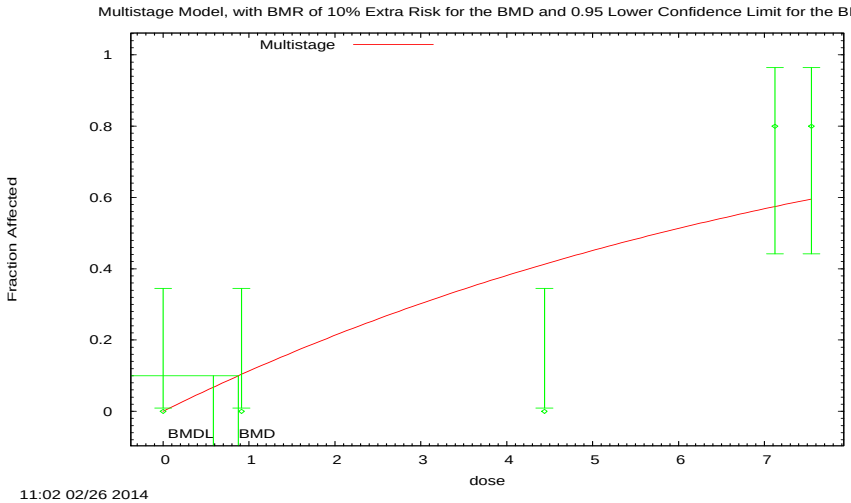

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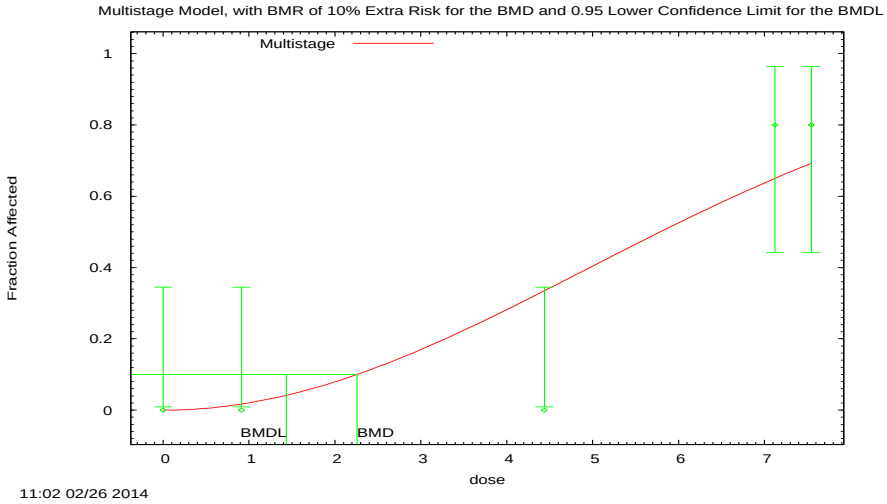

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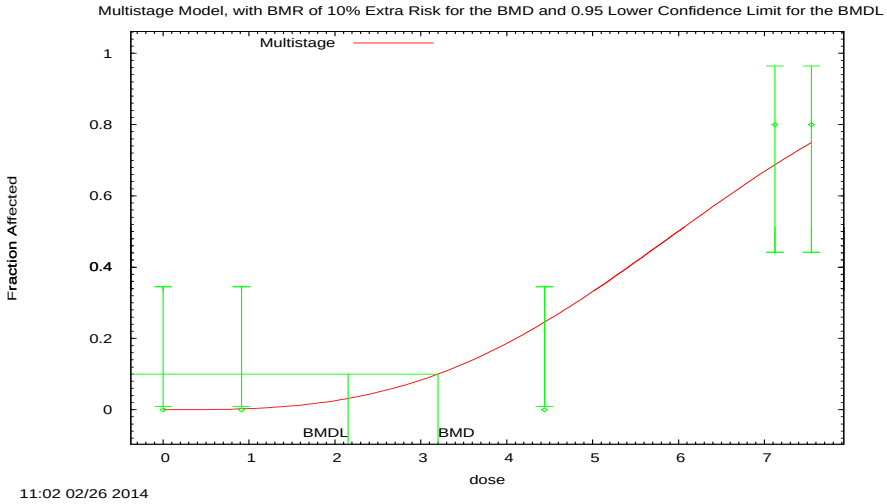

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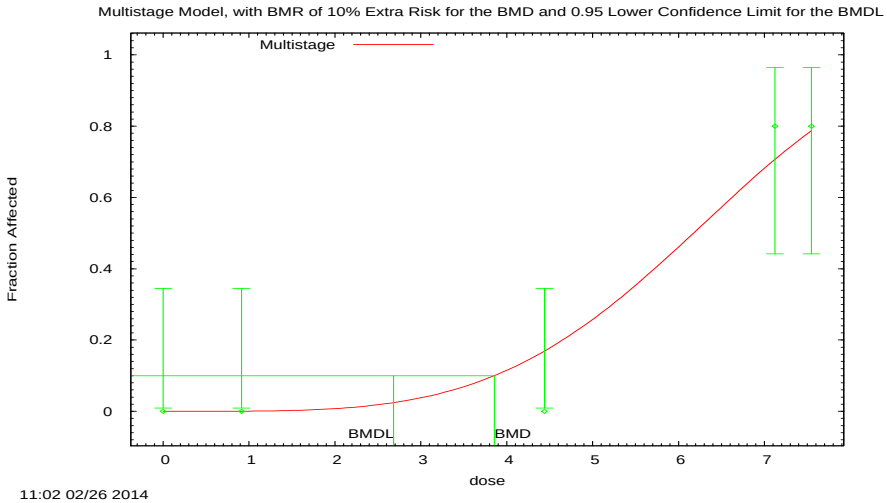

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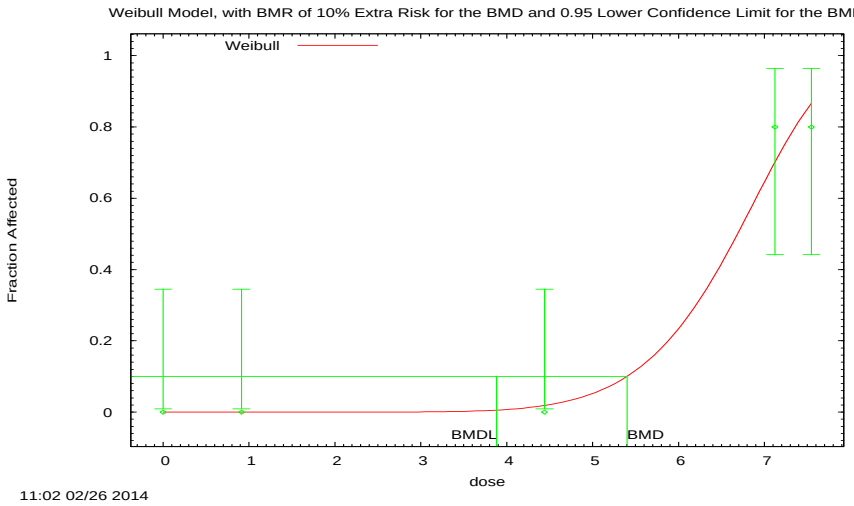

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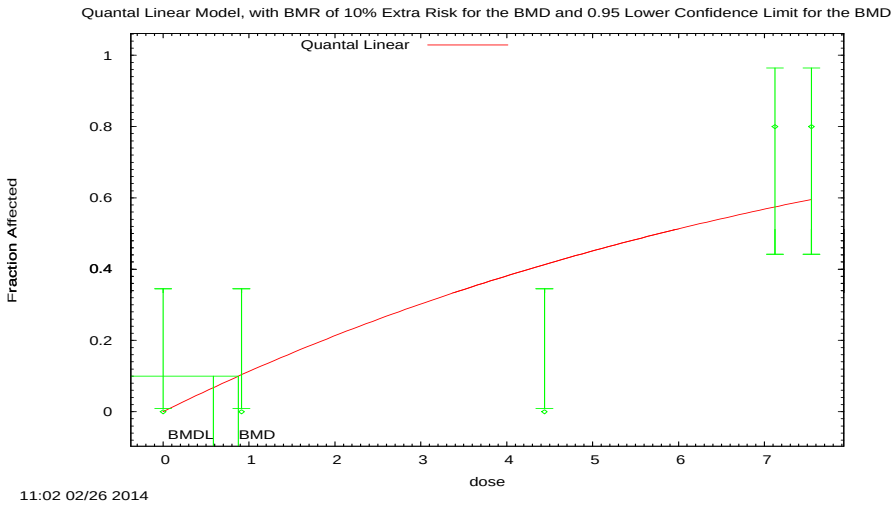

Report:
Experimental Pathology Laboratories, Inc. (2011). 90-Day Inhalation Toxicity Study of Naphthalene Vapor in Fischer 344 Rats. Submitted to The Hamner Institues for Health Sciences, January 31.

APPENDIX 4

Histopathology Report (62 pages)

90-DAY INHALATION TOXICITY STUDY OF NAPHTHALENE VAPOR IN FISCHER 344 RATS

THE HAMNER INSTITUTES FOR HEALTH SCIENCES STUDY ID: 09001

EPL PROJECT NO. 304-440

FINAL PATHOLOGY REPORT

Submitted to:

The Hamner Institutes for Health Sciences
6 Davis Drive
P.O. Box 12137
Research Triangle Park, NC 27709-2137

Submitted by:

Experimental Pathology Laboratories, Inc.
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January 31, 2011

90-DAY INHALATION TOXICITY STUDY OF NAPHTHALENE VAPOR IN FISCHER 344 RATS

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FINAL PATHOLOGY REPORT

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Hamner Study ID: 09001
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90-DAY INHALATION TOXICITY STUDY OF NAPHTHALENE VAPOR IN FISCHER 344 RATS

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INTRODUCTION

The primary objective of this study was to establish an exposure-response relationship for nasal epithelial effects in Fischer 344 (F344) rats in a 90-day study using whole body exposures of 6 hours/day, 5 days/week to naphthalene vapor at concentrations of 0 ppm, 0.1 ppm, 1.0 ppm, 10 ppm or 30 ppm. To determine and evaluate recovery from any effects, groups of similarly exposed rats were necropsied and evaluated after a recovery period of 4 weeks.

METHODS

Six standard nose sections (Morgan, et. al, 1993) were processed and stained with H&E stains and evaluated by light microscopy. The sections (from anterior to posterior) are labeled Tip, Level 1, Level 2, Level 3, Level 4 and Level 5. The Tip and Level 1 have mostly squamous and respiratory epithelium. Olfactory epithelium is first observed along the dorsal meatus of Level 2. Level 3 has olfactory epithelium lining the dorsal meatus, dorsal tips of an ethmoid turbinate first appearing in the dorsal meatus lumen and sometimes low in the nasal septum (the tiny "septal olfactory organ" which is also referred to as the Organ of Masera), the Levels 4 and 5 have mostly olfactory epithelium dorsally lining the meatus, ethmoid turbinates and most of the nasal septum.

TABLE 1. EXPERIMENTAL DESIGN – ANIMAL DISPOSITION

Naphthalene Concentration	Group	Animal Numbers	
		Male	Female
0 ppm	Control (1)	101-110 (Core) 111-120 (Recovery)	301-310 (Core) 311-320 (Recovery)
0.1 ppm	Low (2)	136-145 (Core) 146-155 (Recovery)	336-345 (Core) 346-355 (Recovery)
1.0 ppm	Intermediate Low (3)	171-180 (Core) 181-190 (Recovery)	371-380 (Core) 381-390 (Recovery)
10 ppm	Intermediate High (4)	206-215 (Core) 216-225 (Recovery)	406-415 (Core) 416-425 (Recovery)
30 ppm	High (5)	241-250 (Core) 215-260 (Recovery)	441-450 (Core) 451-460 (Recovery

TABLE 2. SUMMARY OF EXPERIMENTAL DESIGN

	Number of rats/sex	
Concentration (Naphthalene)	Necropsy 1 Day Post Exposure	Necropsy 4 Weeks Post Exposure
Control	10	10
Low (0.1 ppm)	10	10
Intermediate Low (1.0 ppm)	10	10
Intermediate High (10 ppm)	10	10
High (30 ppm)	10	10

RESULTS

The appended tables contain the complete individual animal Histopathology Incidence Tables (HITs) and the Summary Incidence Tables (SITs). Tables 3 – 14 summarize selected histological findings in the nose.

Lesions that could be related to exposure to naphthalene were not observed in the Nose Level Tip and Nose Level 1 of male or female rats. The variable and often prominent mixed inflammatory cell infiltrates commonly present in these two anterior sections were not related to naphthalene exposure. Occasionally, there appeared to be a hair shaft present in the inflamed nasal tissues, otherwise a cause could not be determined.

More posterior (Level 2), lesions related to exposure to naphthalene were clearly observed in the transitional/respiratory epithelium of male and female F344 rats. These changes were observed in the transitional/respiratory epithelium of the lateral walls of Nose Level 2 and characterized by an increase in the thickness of the epithelium (from a normal 1 cell

layer of cuboidal or low columnar epithelia to 2-3 cell layers thick with an increased basophilic appearance). In rats exposed to 1 ppm the transitional/respiratory epithelium was minimally hyperplastic in males and females and that epithelium was minimally to mildly hyperplastic when they were exposed to 10 ppm or 30 ppm. Rats exposed to 10 ppm or 30 ppm commonly also had minimal squamous metaplasia (the superficial epithelial cell layer being horizontal to the basement membrane) of the transitional/respiratory epithelium of the same region. Male and female rats in the 1 ppm, 10 ppm and 30 ppm recovery groups had remarkable recovery of the squamous metaplasia and hyperplasia of the transitional/respiratory epithelium observed in the lateral wall of Level 2 (only one male from the 10 ppm group had residual minimal epithelial hyperplasia).

TABLE 3. Incidence of Transitional/Respiratory Epithelial Hyperplasia in Males - Core

	Control	0.1 ppm	1.0 ppm	10 ppm	30 ppm
Nose level 2	0/10	0/10	10/10	10/10	10/10

TABLE 4. Incidence of Transitional/Respiratory Epithelial Hyperplasia in Males - Recovery

	Control	0.1 ppm	1.0 ppm	10 ppm	30 ppm
Nose level 2	0/10	0/10	0/10	1/9	0/10

TABLE 5. Incidence of Transitional/Respiratory Epithelial Hyperplasia in Females - Core

	Control	0.1 ppm	1.0 ppm	10 ppm	30 ppm
Nose level 2	0/10	0/10	10/10	9/10	9/10

TABLE 6. Incidence of Transitional/Respiratory Epithelial Hyperplasia in Females - Recovery

	Control	0.1 ppm	1.0 ppm	10 ppm	30 ppm
Nose level 2	0/10	0/10	0/10	0/10	0/10

The olfactory epithelial degeneration that was observed at 1 ppm in the two previous studies (1-day and 5-day) was not evident in this study. Sections of nose did not consistently contain the nasal septal organ on Level 3 (the most sensitive location observed in the prior two

studies). When sections of nasal septal organs were present, no changes could be appreciated regardless of exposure group.

The other lesions clearly related to exposure to naphthalene were observed in the olfactory epithelium. These changes were diagnosed as olfactory epithelial degeneration/necrosis. Among the predominately degenerative lesions was evidence of prior and ongoing necrosis. The lesions were generally multifocal and were characterized by cytoplasmic vacuolation, loss of proper epithelial orientation, thinning of the epithelial layer due to decreased olfactory epithelial cells, pkynotic and karyorrhectic nuclei and occasionally sloughing of the epithelium. There were some areas of re-epithelialization, beneath the sloughed epithelium, that sometimes covered the surface with flattened cells similar to squamous cells but not layered enough to call squamous metaplasia in most cases. Occasionally respiratory epithelial metaplasia of the olfactory epithelium (columnar ciliated cells replacing olfactory epithelium) was observed as a sequel to the degeneration and necrosis that had occurred. Minimal mixed inflammatory cell infiltration was present in the lamina propria and occasionally neutrophils were seen free in the nasal lumen.

Associated with the degenerative changes in the olfactory epithelium was basal cell hyperplasia characterized by increase numbers of basal cells per unit length of the epithelium underlying the olfactory neurons and sustentacular cells. The basal cells often became rounded (instead of flattened), crowded, and frequently oriented perpendicular to the basement membrane. Often the basal cell nuclei were double to triple-layered and occasionally a few small foci could be seen deeper in the lamina propria.

Overall, the induced olfactory epithelial changes were relatively consistent in incidence and severity between male and female F344 rats.

Neither sex of F344 rats exposed to 0.1 ppm or 1. 0 ppm of naphthalene had lesions related to exposure in the olfactory epithelium.

In rats exposed to 10 ppm of naphthalene and sacrificed one day after the end of exposure, prominent olfactory epithelial lesions were evident in all male and female F344 rats in most nose sections in all nose levels (2, 3, 4, and 5) containing olfactory epithelium. The olfactory lesions were similar in male and female rats. Most of the olfactory epithelium lining the dorsal meatus of Level 2 was degenerative, which consisted of a prominent loss of neuronal cells and disorganization of residual sustentacular cells. In this 10 ppm group, the Level 3

sections now had lesions observed extensively in the dorsal meatus. The olfactory epithelium of Levels 4 and 5 had multifocal to confluent areas of degeneration/necrosis located in the dorsal meatus, along the nasal septum, in ethmoid turbinates in proximity to the septum and multifocally in the ethmoid turbinate lateral aspects.

In general, the olfactory epithelial degeneration/necrosis was associated with a relatively inconspicuous mixed cell inflammation that was not diagnosed separately.

The rats exposed to 10 ppm of naphthalene and allowed to recover for 4 weeks all showed a similar remarkable degree of olfactory neuron recovery, but most still had evidence of residual olfactory epithelial degeneration. Many lesions seem to have repopulated with neuronal cells but remained minimally thinner (fewer cells in some areas), contained scattered rosettes, and had minimally disorganized foci in previously affected locations: nasal septum, dorsal meatus and ethmoid turbinates. Recovery appeared to be more complete in the more posterior sections that contained olfactory epithelium. Basal cell hyperplasia recovery seemed to lag olfactory neuron recovery. Most olfactory epithelial inflammatory changes were resolved.

The male and female rats exposed to 30 ppm of naphthalene had olfactory lesions that were qualitatively similar to those rats exposed to 10 ppm, but somewhat more severe. Recovery of the olfactory epithelium occurred, but was not as pronounced as seen at 10 ppm. Recovery appeared to be more complete in the more posterior sections that contained olfactory epithelium and again the basal cell hyperplasia recovery appeared to lag behind the olfactory neuronal recovery.

Table _7_. Incidence of Olfactory Epithelial Degeneration/Necrosis in Males – Core

	Control	0.1 ppm	1.0 ppm	10 ppm	30 ppm
Nose Level 2	0/10	0/10	0/10	8/10	10/10
Nose Level 3	0/10	0/10	0/10	10/10	10/10
Nose Level 4	0/10	0/10	0/10	10/10	10/10
Nose Level 5	0/10	0/10	0/10	9/10	10/10

Table _8_. Incidence of Olfactory Epithelial Degeneration/Necrosis in Males - Recovery

	Control	0.1 ppm	1.0 ppm	10 ppm	30 ppm
Nose Level 2	0/10	0/10	0/10	6/9	8/10
Nose Level 3	0/10	0/10	0/10	9/9	10/10
Nose Level 4	0/10	0/10	0/10	8/9	10/10
Nose Level 5	0/10	0/10	0/10	0/9	6/10

Table 9 Incidence of Olfactory Epithelial Degeneration/Necrosis in Females – Core

	Control	0.1 ppm	1.0 ppm	10 ppm	30 ppm
Nose Level 2	0/10	0/10	0/10	10/10	10/10
Nose Level 3	0/10	0/10	0/10	10/10	10/10
Nose Level 4	0/10	0/10	0/10	10/10	10/10
Nose Level 5	0/10	0/10	0/10	9/10	10/10

Table 10 Incidence of Olfactory Epithelial Degeneration/Necrosis in Females – Recovery

	Control	0.1 ppm	1.0 ppm	10 ppm	30 ppm
Nose Level 2	0/10	0/10	0/10	5/10	8/10
Nose Level 3	0/10	0/10	0/10	8/10	10/10
Nose Level 4	0/10	0/10	0/10	7/10	10/10
Nose Level 5	0/10	0/10	0/10	2/10	7/10

Table 11 Incidence of Olfactory Epithelial Basal Cell Hyperplasia in Males – Core

	Control	0.1 ppm	1.0 ppm	10 ppm	30 ppm
Nose Level 2	0/10	0/10	0/10	7/10	10/10
Nose Level 3	0/10	0/10	0/10	8/10	10/10
Nose Level 4	0/10	0/10	0/10	9/10	10/10
Nose Level 5	0/10	0/10	0/10	6/10	10/10

Table 12 Incidence of Olfactory Epithelial Basal Cell Hyperplasia in Males – Recovery

	Control	0.1 ppm	1.0 ppm	10 ppm	30 ppm
Nose Level 2	0/10	0/10	0/10	8/9	8/10
Nose Level 3	0/10	0/10	0/10	7/9	10/10
Nose Level 4	0/10	0/10	0/10	6/9	10/10
Nose Level 5	0/10	0/10	0/10	2/9	9/10

Table 13 Incidence of Olfactory Epithelial Basal Cell Hyperplasia in Females – Core

	Control	0.1 ppm	1.0 ppm	10 ppm	30 ppm
Nose Level 2	0/10	0/10	0/10	10/10	10/10
Nose Level 3	0/10	0/10	0/10	10/10	10/10
Nose Level 4	0/10	0/10	0/10	10/10	10/10
Nose Level 5	0/10	0/10	0/10	9/10	10/10

Table 14 Incidence of Olfactory Epithelial Basal Cell Hyperplasia Females – Recovery

	Control	0.1 ppm	1.0 ppm	10 ppm	30 ppm
Nose Level 2	0/10	0/10	0/10	6/10	8/10
Nose Level 3	0/10	0/10	0/10	10/10	10/10
Nose Level 4	0/10	0/10	0/10	10/10	10/10
Nose Level 5	0/10	0/10	0/10	6/10	10/10

An ancillary observation was recorded in some rats exposed to 1 ppm, 10 ppm, or 30 ppm of naphthalene. Nasopharyngeal duct goblet cell hyperplasia/hypertrophy appeared marginally related to exposure and was graded as minimal. It was diagnosed in 1 male exposed to 1 ppm, 5 females and 1 male exposed to 10 ppm, and 7 females and 5 males exposed to 30 ppm. In the 4 week recovery rats, it appeared as a residual lesion in only 1 male exposed to 10 ppm, and in 3 females that were exposed to 30 ppm.

SUMMARY

Lesions clearly related to exposure to naphthalene were observed in the transitional/respiratory epithelium and in the olfactory epithelium. These changes were diagnosed as transitional/respiratory epithelial hyperplasia and squamous metaplasia. The olfactory epithelium had degeneration/necrosis and olfactory epithelial basal cell hyperplasia. Goblet cell hypertropy/hyperplasia of the nasopharngeal duct was a possible exposure related effect evident at the higher exposure levels.

Overall, the induced olfactory epithelial changes were relatively consistent in incidence and severity among male and female rats.

Female and male F344 rats exposed to 0.1 ppm or 1 ppm of naphthalene had no lesions in the olfactory epithelium.

In rats exposed to 1 ppm of naphthalene lesions related to exposure to naphthalene were only observed in the transitional/respiratory epithelium of the lateral wall of Nasal Level 2.

In rats exposed to 10 ppm and 30 ppm of naphthalene and sacrificed one day after the end of exposure had prominent olfactory epithelial lesions in male and female F344 rats in most nose sections in all nose levels (2, 3, 4, and 5) containing olfactory epithelium. The olfactory lesions were similar in these rats. Most of the olfactory epithelium lining the dorsal meatus of Level 2 was affected. In these two highest exposure groups, the Level 3 sections had lesions observed in the dorsal meatus. The olfactory epithelium of Levels 4 and 5 had multifocal to

confluent areas of degeneration located in the dorsal meatus, along the nasal septum, in ethmoid turbinates in proximity to the septum and multifocally in the ethmoid turbinate lateral aspects.

Rats exposed to naphthalene and then allowed to recover for 4 weeks, all showed a similar and remarkable degree of olfactory epithelial recovery, but most still had evidence of minimal residual olfactory epithelial degeneration. Basal cell hyperplasia underlying the olfactory epithelium was a lessened lesion but still an obvious change from normal.

Rodney A. Miller

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Veterinary Pathologist

1-31-11
Date

RAM/dc

REFERENCE:

Morgan, K. T., Gross, E. A., Bonnefoi, M. 1993. Nasal structure, function, and toxicology. Chapter 2 in *Toxicology of the Lung* 2nd ed., D. E. Gardner et al. New York: Raven Press, Ltd.

Hamner Study ID: 09001
EPL Project No.: 304-440
FINAL REPORT – January 31, 2011

COMPLIANCE STATEMENT

Client Name	The Hamner Institutes for Health Sciences	EPL Principal Investigator	Dr. Gabrielle Willson
Client Study	Protocol No. 09001	EPL Pathologist	Dr. Rodney Miller
Species	Fischer 344 Rats	EPL Project Number	304-440

Study Title: 90-Day Inhalation Toxicity Study of Naphthalene Vapor in Fischer 344 Rats

Test Article: Naphthalene

The tissue histopathology (H&E) evaluations were conducted in compliance with U.S. EPA Toxic Substances Control Act (TSCA) Good Laboratory Practices (GLP) as noted in Title 40 CFR Part 792.

EPL Principal Investigator

31st January 2011
Date

QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: 90-Day Inhalation Toxicity Study of Naphthalene Vapor in Fischer 344 Rats

Client Study: Protocol No. 09001

EPL Principal Investigator: Dr. Gabrielle Willson

EPL Project Number: 304-440

EPL Pathologist: Dr. Rodney Miller

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the EPL Principal Investigator and Management are indicated below.

	Dates	
Area Inspected	Inspection	Reporting
EPL Project Sheets	March 19, 2009; October 14, 2009; September 30, 2010	March 19, 2009; October 14, 2009; September 30, 2010
Project Setup	November 20 & 30. 2009	November 30, 2009
Data Review	July 6, 2010	July 6, 2010
Draft Pathology Report	December 3, 2009	December 3, 2009
Final Pathology Report	January 31, 2011	January 31, 2011

Date reported to Study Director/Management	January 31, 2011
Date of last quarterly facility inspection:	January 2011

Janet Hollingsworth
EPL Quality Assurance Unit

January 31, 2011
Date

90-DAY SACRIFICE

PROTOCOL NO. 09001
EPL PROJECT NO. 304-440

SUMMARY INCIDENCE TABLES
90-Day Sacrifice

SUMMARY INCIDENCE TABLE

09001
90-Day Sacrifice
Male Rat

	GROUP 0ppm	GROUP 0.1ppm	GROUP 1.0ppm	GROUP 10ppm	GROUP 30ppm	
Nose, Level 1 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Transitional/Respiratory						
Epithelium, Hyperplasia	1	1	2			
Transitional/Respiratory						
Epithelium, Inflammation	6	6	5	5	4	
Transitional/Respiratory						
Epithelium, Squamous,						
Metaplasia	1	1				
Nose, Level 2 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				7	10	
Olfactory Epithelium,						
Degeneration/Necrosis				8	10	
Olfactory Epithelium,						
Inflammation					1	
Transitional/Respiratory						
Epithelium, Hyperplasia			10	10	10	
Transitional/Respiratory						
Epithelium, Inflammation				1		
Transitional/Respiratory						
Epithelium, Squamous,						
Metaplasia				8	8	
Nose, Level 3 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				8	10	
Olfactory Epithelium,						
Degeneration/Necrosis				10	10	
Nose, Level 4 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				9	10	
Olfactory Epithelium,						
Degeneration/Necrosis				10	10	
Olfactory Epithelium,						
Inflammation					1	
Olfactory Epithelium,						
Squamous, Hyperplasia					1	
Nose, Level 5 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Nasopharyngeal Duct, Goblet						
Cell, Hypertrophy/Hyperplasia			1	1	5	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				6	10	

SUMMARY INCIDENCE TABLE

09001
90-Day Sacrifice
Male Rat

	GROUP 0ppm	GROUP 0.1ppm	GROUP 1.0ppm	GROUP 10ppm	GROUP 30ppm	
Nose, Level 5 (CONTINUED)						
Olfactory Epithelium,						
Degeneration/Necrosis				9	10	
Olfactory Epithelium,						
Squamous, Metaplasia					1	
Nose, Tip (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Squamous Epithelium,						
Hyperplasia	2					
Squamous Epithelium,						
Inflammation	5	6	3	5	4	

SUMMARY INCIDENCE TABLE

09001
90-Day Sacrifice
Female Rat

	GROUP 0ppm	GROUP 0.1ppm	GROUP 1.0ppm	GROUP 10ppm	GROUP 30ppm	
Nose, Level 1 (NO. EXAMINED)	(10)	(10)	(10)	(9)	(10)	
Transitional/Respiratory						
Epithelium, Hyperplasia						
Transitional/Respiratory						
Epithelium, Inflammation	9	8	8	6	8	
Transitional/Respiratory						
Epithelium, Squamous,						
Metaplasia						
Nose, Level 2 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				10	10	
Olfactory Epithelium,						
Degeneration/Necrosis				10	10	
Olfactory Epithelium,						
Inflammation						
Transitional/Respiratory						
Epithelium, Hyperplasia			10	9	9	
Transitional/Respiratory						
Epithelium, Inflammation						
Transitional/Respiratory						
Epithelium, Squamous,						
Metaplasia				9	8	
Nose, Level 3 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				10	10	
Olfactory Epithelium,						
Degeneration/Necrosis				10	10	
Nose, Level 4 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				10	10	
Olfactory Epithelium,						
Degeneration/Necrosis				10	10	
Olfactory Epithelium,						
Inflammation						
Olfactory Epithelium,						
Squamous, Hyperplasia						
Nose, Level 5 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Nasopharyngeal Duct, Goblet						
Cell, Hypertrophy/Hyperplasia				5	7	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				9	10	

SUMMARY INCIDENCE TABLE

09001
90-Day Sacrifice
Female Rat

	GROUP 0ppm	GROUP 0.1ppm	GROUP 1.0ppm	GROUP 10ppm	GROUP 30ppm	
Nose, Level 5 (CONTINUED)						
Olfactory Epithelium,						
Degeneration/Necrosis				9	10	
Olfactory Epithelium,						
Squamous, Metaplasia						
Nose, Tip (NO. EXAMINED)	(10)	(10)	(10)	(9)	(10)	
Squamous Epithelium,						
Hyperplasia						
Squamous Epithelium,						
Inflammation	10	9	8	7	10	

HISTOPATHOLOGY INCIDENCE TABLES
90-Day Sacrifice

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Male Rat

	GROUP 0ppm																			
ANIMAL	101	102	103	104	105	106	107	108	109	110										
Nose, Level 1	X		X	X				X												
Transitional/Respiratory																				
Epithelium, Hyperplasia		1																		
Transitional/Respiratory																				
Epithelium, Inflammation		1			1	1	2		2	1										
Transitional/Respiratory																				
Epithelium, Squamous,																				
Metaplasia		1																		
Nose, Level 2	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Olfactory Epithelium,																				
Inflammation																				
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation																				
Transitional/Respiratory																				
Epithelium, Squamous,																				
Metaplasia																				
Nose, Level 3	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Nose, Level 4	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Olfactory Epithelium,																				
Inflammation																				
Olfactory Epithelium,																				
Squamous, Hyperplasia																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Male Rat

GROUP
0ppm

ANIMAL	101	102	103	104	105	106	107	108	109	110
Nose, Level 5	X	X	X	X	X	X	X	X	X	X
Nasopharyngeal Duct, Goblet Cell, Hypertrophy/Hyperplasia										
Olfactory Epithelium, Basal Cell, Hyperplasia										
Olfactory Epithelium, Degeneration/Necrosis										
Olfactory Epithelium, Squamous, Metaplasia										
Nose, Tip	X	X					X	X	X	
Squamous Epithelium, Hyperplasia			1		1					
Squamous Epithelium, Inflammation			1	1	2	1				1

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Male Rat

GROUP
0.1ppm

ANIMAL	136	137	138	139	140	141	142	143	144	145
Nose, Level 1			X			X	X			X
Transitional/Respiratory Epithelium, Hyperplasia					1					
Transitional/Respiratory Epithelium, Inflammation	2	1		1	2			2	1	
Transitional/Respiratory Epithelium, Squamous, Metaplasia					1					
Nose, Level 2	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal Cell, Hyperplasia										
Olfactory Epithelium, Degeneration/Necrosis										
Olfactory Epithelium, Inflammation										
Transitional/Respiratory Epithelium, Hyperplasia										
Transitional/Respiratory Epithelium, Inflammation										
Transitional/Respiratory Epithelium, Squamous, Metaplasia										
Nose, Level 3	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal Cell, Hyperplasia										
Olfactory Epithelium, Degeneration/Necrosis										
Nose, Level 4	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal Cell, Hyperplasia										
Olfactory Epithelium, Degeneration/Necrosis										
Olfactory Epithelium, Inflammation										
Olfactory Epithelium, Squamous, Hyperplasia										

Key : X-Not Remarkable N-No Section I-Incomplete A-Autolysis
1-minimal 2-slight/mild 3-moderate 4-moderately severe 5-severe/high
P-Present B-Benign M-Malignant
m-missing one paired organ u-unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Male Rat

GROUP
0.1ppm

ANIMAL	136	137	138	139	140	141	142	143	144	145
Nose, Level 5	X	X	X	X	X	X	X	X	X	X
Nasopharyngeal Duct, Goblet Cell, Hypertrophy/Hyperplasia										
Olfactory Epithelium, Basal Cell, Hyperplasia										
Olfactory Epithelium, Degeneration/Necrosis										
Olfactory Epithelium, Squamous, Metaplasia										
Nose, Tip	X				X	X	X			
Squamous Epithelium, Hyperplasia										
Squamous Epithelium, Inflammation		2	2	2				2	1	2

Key : X-Not Remarkable N-No Section I-Incomplete A-Autolysis
1-minimal 2-slight/mild 3-moderate 4-moderately severe 5-severe/high
P-Present B-Benign M-Malignant
m-missing one paired organ u-unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Male Rat

GROUP
1.0ppm

ANIMAL	171	172	173	174	175	176	177	178	179	180
Nose, Level 1		X	X	X			X	X		
Transitional/Respiratory										
Epithelium, Hyperplasia	1					1				
Transitional/Respiratory										
Epithelium, Inflammation	2				2	1			1	2
Transitional/Respiratory										
Epithelium, Squamous,										
Metaplasia										
Nose, Level 2										
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										
Olfactory Epithelium,										
Inflammation										
Transitional/Respiratory										
Epithelium, Hyperplasia	1	1	1	1	1	1	1	1	1	1
Transitional/Respiratory										
Epithelium, Inflammation										
Transitional/Respiratory										
Epithelium, Squamous,										
Metaplasia										
Nose, Level 3	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										
Nose, Level 4	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										
Olfactory Epithelium,										
Inflammation										
Olfactory Epithelium,										
Squamous, Hyperplasia										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Male Rat

GROUP
1.0ppm

	ANIMAL																			
	171	172	173	174	175	176	177	178	179	180										
Nose, Level 5	X		X	X	X	X	X	X	X	X										
Nasopharyngeal Duct, Goblet																				
Cell, Hypertrophy/Hyperplasia		1																		
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Olfactory Epithelium,																				
Squamous, Metaplasia																				
Nose, Tip	X	X	X	X		X	X	X												
Squamous Epithelium,																				
Hyperplasia																				
Squamous Epithelium,																				
Inflammation					2				1	2										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Male Rat

	GROUP 10ppm																			
ANIMAL	206	207	208	209	210	211	212	213	214	215										
Nose, Level 1			X	X	X				X	X										
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation	1	1				2	1	1												
Transitional/Respiratory																				
Epithelium, Squamous,																				
Metaplasia																				
Nose, Level 2																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	1	1	1	2				1	2										
Olfactory Epithelium,																				
Degeneration/Necrosis	2	2	2	1	2		2		2	2										
Olfactory Epithelium,																				
Inflammation																				
Transitional/Respiratory																				
Epithelium, Hyperplasia	1	2	2	2	1	1	1	2	1	1										
Transitional/Respiratory																				
Epithelium, Inflammation						1														
Transitional/Respiratory																				
Epithelium, Squamous,																				
Metaplasia	2	1		1		1	1	1	1	1										
Nose, Level 3																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	1	1	1	1	1			1	1	1										
Olfactory Epithelium,																				
Degeneration/Necrosis	1	1	2	2	2	1	1	2	1	1										
Nose, Level 4																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	1	1	1	1	2		1	1	1	1										
Olfactory Epithelium,																				
Degeneration/Necrosis	2	2	2	2	2	1	2	2	3	2										
Olfactory Epithelium,																				
Inflammation																				
Olfactory Epithelium,																				
Squamous, Hyperplasia																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Male Rat

GROUP
10ppm

	ANIMAL 206	207	208	209	210	211	212	213	214	215
Nose, Level 5		X								
Nasopharyngeal Duct, Goblet										
Cell, Hypertrophy/Hyperplasia										1
Olfactory Epithelium, Basal										
Cell, Hyperplasia	1		1	1	1			1	1	
Olfactory Epithelium,										
Degeneration/Necrosis	1		1	1	1	1	1	2	1	2
Olfactory Epithelium,										
Squamous, Metaplasia										
Nose, Tip			X	X				X	X	X
Squamous Epithelium,										
Hyperplasia										
Squamous Epithelium,										
Inflammation	1	1			1	2	2			

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Male Rat

	GROUP 30ppm																			
ANIMAL	241	242	243	244	245	246	247	248	249	250										
Nose, Level 1	X	X		X			X	X	X											
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation			1		1	1				1										
Transitional/Respiratory																				
Epithelium, Squamous,																				
Metaplasia																				
Nose, Level 2																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	2	2	2	1	2	2	1	2	1										
Olfactory Epithelium,																				
Degeneration/Necrosis	2	2	2	2	1	2	2	1	2	1										
Olfactory Epithelium,																				
Inflammation	1																			
Transitional/Respiratory																				
Epithelium, Hyperplasia	1	2	2	2	1	1	1	2	1	1										
Transitional/Respiratory																				
Epithelium, Inflammation																				
Transitional/Respiratory																				
Epithelium, Squamous,																				
Metaplasia			1	1	1	1	1	1	1	1										
Nose, Level 3																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	2	1	2	2	2	2	2	2	2										
Olfactory Epithelium,																				
Degeneration/Necrosis	2	2	3	2	2	2	3	2	2	3										
Nose, Level 4																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	2	3	2	2	2	2	2	2	2										
Olfactory Epithelium,																				
Degeneration/Necrosis	2	2	3	3	2	3	3	3	3	3										
Olfactory Epithelium,																				
Inflammation							1													
Olfactory Epithelium,																				
Squamous, Hyperplasia									2											

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Male Rat

GROUP
30ppm

ANIMAL	241	242	243	244	245	246	247	248	249	250
Nose, Level 5										
Nasopharyngeal Duct, Goblet										
Cell, Hypertrophy/Hyperplasia	1		1					1	1	1
Olfactory Epithelium, Basal										
Cell, Hyperplasia	2	2	2	2	2	2	2	2	2	2
Olfactory Epithelium,										
Degeneration/Necrosis	2	2	2	2	1	1	2	2	2	2
Olfactory Epithelium,										
Squamous, Metaplasia	1									
Nose, Tip	X	X	X				X	X	X	
Squamous Epithelium,										
Hyperplasia										
Squamous Epithelium,										
Inflammation				1	1	1				1

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Female Rat

GROUP
0ppm

ANIMAL	301	302	303	304	305	306	307	308	309	310
Nose, Level 1										X
Transitional/Respiratory										
Epithelium, Hyperplasia										
Transitional/Respiratory										
Epithelium, Inflammation	2	2	3	2	2	3	2	1	2	
Transitional/Respiratory										
Epithelium, Squamous,										
Metaplasia										
Nose, Level 2	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										
Olfactory Epithelium,										
Inflammation										
Transitional/Respiratory										
Epithelium, Hyperplasia										
Transitional/Respiratory										
Epithelium, Inflammation										
Transitional/Respiratory										
Epithelium, Squamous,										
Metaplasia										
Nose, Level 3	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										
Nose, Level 4	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										
Olfactory Epithelium,										
Inflammation										
Olfactory Epithelium,										
Squamous, Hyperplasia										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Female Rat

	GROUP 0ppm																			
ANIMAL	301	302	303	304	305	306	307	308	309	310										
Nose, Level 5	X	X	X	X	X	X	X	X	X	X										
Nasopharyngeal Duct, Goblet																				
Cell, Hypertrophy/Hyperplasia																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Olfactory Epithelium,																				
Squamous, Metaplasia																				
Nose, Tip																				
Squamous Epithelium,																				
Hyperplasia																				
Squamous Epithelium,																				
Inflammation	2	1	3	2	3	2	2	1	2	1										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Female Rat

	GROUP 0.1ppm																			
ANIMAL	336	337	338	339	340	341	342	343	344	345										
Nose, Level 1			X							X										
Transitional/Respiratory Epithelium, Hyperplasia																				
Transitional/Respiratory Epithelium, Inflammation	1	2		3	2	1	2	1	2											
Transitional/Respiratory Epithelium, Squamous, Metaplasia																				
Nose, Level 2	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal Cell, Hyperplasia																				
Olfactory Epithelium, Degeneration/Necrosis																				
Olfactory Epithelium, Inflammation																				
Transitional/Respiratory Epithelium, Hyperplasia																				
Transitional/Respiratory Epithelium, Inflammation																				
Transitional/Respiratory Epithelium, Squamous, Metaplasia																				
Nose, Level 3	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal Cell, Hyperplasia																				
Olfactory Epithelium, Degeneration/Necrosis																				
Nose, Level 4	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal Cell, Hyperplasia																				
Olfactory Epithelium, Degeneration/Necrosis																				
Olfactory Epithelium, Inflammation																				
Olfactory Epithelium, Squamous, Hyperplasia																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Female Rat

GROUP
0.1ppm

ANIMAL	336	337	338	339	340	341	342	343	344	345
Nose, Level 5	X	X	X	X	X	X	X	X	X	X
Nasopharyngeal Duct, Goblet Cell, Hypertrophy/Hyperplasia										
Olfactory Epithelium, Basal Cell, Hyperplasia										
Olfactory Epithelium, Degeneration/Necrosis										
Olfactory Epithelium, Squamous, Metaplasia										
Nose, Tip			X							
Squamous Epithelium, Hyperplasia										
Squamous Epithelium, Inflammation	1	2		2	2	2	2	2	2	1

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Female Rat

GROUP
1.0ppm

ANIMAL	371	372	373	374	375	376	377	378	379	380
Nose, Level 1					X		X			
Transitional/Respiratory										
Epithelium, Hyperplasia										
Transitional/Respiratory										
Epithelium, Inflammation	3	1	3	1		2		2	1	1
Transitional/Respiratory										
Epithelium, Squamous,										
Metaplasia										
Nose, Level 2										
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										
Olfactory Epithelium,										
Inflammation										
Transitional/Respiratory										
Epithelium, Hyperplasia	1	1	1	1	1	1	1	1	1	1
Transitional/Respiratory										
Epithelium, Inflammation										
Transitional/Respiratory										
Epithelium, Squamous,										
Metaplasia										
Nose, Level 3	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										
Nose, Level 4	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										
Olfactory Epithelium,										
Inflammation										
Olfactory Epithelium,										
Squamous, Hyperplasia										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Female Rat

	GROUP 1.0ppm																			
ANIMAL	371	372	373	374	375	376	377	378	379	380										
Nose, Level 5	X	X	X	X	X	X	X	X	X	X										
Nasopharyngeal Duct, Goblet																				
Cell, Hypertrophy/Hyperplasia																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Olfactory Epithelium,																				
Squamous, Metaplasia																				
Nose, Tip				X	X															
Squamous Epithelium,																				
Hyperplasia																				
Squamous Epithelium,																				
Inflammation	3	1	2			2	1	2	1	1										

Key : X-Not Remarkable N-No Section I-Incomplete A-Autolysis
1-minimal 2-slight/mild 3-moderate 4-moderately severe 5-severe/high
P-Present B-Benign M-Malignant
m-missing one paired organ u-unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Female Rat

	GROUP 10ppm																			
ANIMAL	406	407	408	409	410	411	412	413	414	415										
Nose, Level 1			X	N	X			X												
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation	2	2				2	2		2	1										
Transitional/Respiratory																				
Epithelium, Squamous,																				
Metaplasia																				
Nose, Level 2																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	2	2	1	2	2	2	2	2	2										
Olfactory Epithelium,																				
Degeneration/Necrosis	2	2	2	1	2	2	2	2	2	2										
Olfactory Epithelium,																				
Inflammation																				
Transitional/Respiratory																				
Epithelium, Hyperplasia	2	2	2	2	2	2	1	1	2											
Transitional/Respiratory																				
Epithelium, Inflammation																				
Transitional/Respiratory																				
Epithelium, Squamous,																				
Metaplasia	1	1	1	1	1	1	1	1	1											
Nose, Level 3																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	1	2	1	1	1	1	1	2	2	2										
Olfactory Epithelium,																				
Degeneration/Necrosis	1	2	1	2	2	2	1	2	2	2										
Nose, Level 4																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	2	2	2	2	2	2	2	2	1										
Olfactory Epithelium,																				
Degeneration/Necrosis	2	2	2	3	3	2	2	2	3	2										
Olfactory Epithelium,																				
Inflammation																				
Olfactory Epithelium,																				
Squamous, Hyperplasia																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Female Rat

	GROUP 10ppm																				
ANIMAL	406	407	408	409	410	411	412	413	414	415											
Nose, Level 5			X																		
Nasopharyngeal Duct, Goblet																					
Cell, Hypertrophy/Hyperplasia	1				1	1	1		1												
Olfactory Epithelium, Basal																					
Cell, Hyperplasia	2	1		1	1	1	2	1	2	1											
Olfactory Epithelium,																					
Degeneration/Necrosis	2	1		2	3	1	1	1	3	1											
Olfactory Epithelium,																					
Squamous, Metaplasia																					
Nose, Tip			X	N	X																
Squamous Epithelium,																					
Hyperplasia																					
Squamous Epithelium,																					
Inflammation	2	1				1	2	1	2	1											

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Female Rat

GROUP
30ppm

ANIMAL	441	442	443	444	445	446	447	448	449	450
Nose, Level 1		X			X					
Transitional/Respiratory										
Epithelium, Hyperplasia										
Transitional/Respiratory										
Epithelium, Inflammation	2		2	1		2	1	1	3	2
Transitional/Respiratory										
Epithelium, Squamous,										
Metaplasia										
Nose, Level 2										
Olfactory Epithelium, Basal										
Cell, Hyperplasia	3	3	2	3	2	2	3	2	2	3
Olfactory Epithelium,										
Degeneration/Necrosis	2	2	2	2	2	2	2	2	2	2
Olfactory Epithelium,										
Inflammation										
Transitional/Respiratory										
Epithelium, Hyperplasia	2	2	2	2	1	1	2	2		1
Transitional/Respiratory										
Epithelium, Inflammation										
Transitional/Respiratory										
Epithelium, Squamous,										
Metaplasia	1	1	1	1	1		1	1		1
Nose, Level 3										
Olfactory Epithelium, Basal										
Cell, Hyperplasia	2	2	2	2	2	2	2	2	2	2
Olfactory Epithelium,										
Degeneration/Necrosis	2	2	2	2	2	2	2	2	2	2
Nose, Level 4										
Olfactory Epithelium, Basal										
Cell, Hyperplasia	2	2	2	2	2	2	2	2	2	2
Olfactory Epithelium,										
Degeneration/Necrosis	2	3	2	2	2	2	2	2	2	3
Olfactory Epithelium,										
Inflammation										
Olfactory Epithelium,										
Squamous, Hyperplasia										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
90-Day Sacrifice
Female Rat

GROUP
30ppm

ANIMAL	441	442	443	444	445	446	447	448	449	450										
Nose, Level 5																				
Nasopharyngeal Duct, Goblet																				
Cell, Hypertrophy/Hyperplasia	1	1	1	1			1		1	1										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	2	2	2	2	1	2	1	2	2										
Olfactory Epithelium,																				
Degeneration/Necrosis	1	2	2	2	2	1	2	1	2	2										
Olfactory Epithelium,																				
Squamous, Metaplasia																				
Nose, Tip																				
Squamous Epithelium,																				
Hyperplasia																				
Squamous Epithelium,																				
Inflammation	2	1	1	1	1	2	1	1	3	2										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

RECOVERY SACRIFICE

PROTOCOL NO. 09001
EPL PROJECT NO. 304-440

SUMMARY INCIDENCE TABLES
Recovery Sacrifice

SUMMARY INCIDENCE TABLE

09001
Recovery Sacrifice
Male Rat

	GROUP 0ppm	GROUP 0.1ppm	GROUP 1.0ppm	GROUP 10ppm	GROUP 30ppm	
Nose, Level 1 (NO. EXAMINED)	(10)	(10)	(10)	(9)	(10)	
Transitional/Respiratory						
Epithelium, Hyperplasia	1					
Transitional/Respiratory						
Epithelium, Inflammation	5	6	6	8	8	
Nose, Level 2 (NO. EXAMINED)	(10)	(10)	(10)	(9)	(10)	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				8	8	
Olfactory Epithelium,						
Degeneration/Necrosis				6	8	
Transitional/Respiratory						
Epithelium, Hyperplasia				1		
Transitional/Respiratory						
Epithelium, Inflammation						
Nose, Level 3 (NO. EXAMINED)	(10)	(10)	(10)	(9)	(10)	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				7	10	
Olfactory Epithelium,						
Degeneration/Necrosis				9	10	
Respiratory Epithelium,						
Inflammation	2					
Nose, Level 4 (NO. EXAMINED)	(10)	(10)	(10)	(9)	(10)	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				6	10	
Olfactory Epithelium,						
Degeneration/Necrosis				8	10	
Olfactory Epithelium,						
Inflammation					1	
Nose, Level 5 (NO. EXAMINED)	(10)	(10)	(10)	(9)	(10)	
Nasopharyngeal Duct, Goblet						
Cell, Hypertrophy/Hyperplasia				1		
Olfactory Epithelium, Basal						
Cell, Hyperplasia				2	9	
Olfactory Epithelium,						
Degeneration/Necrosis					6	
Nose, Tip (NO. EXAMINED)	(10)	(10)	(10)	(9)	(10)	
Squamous Epithelium,						
Hyperplasia	1					
Squamous Epithelium,						
Inflammation	5	4	3	7	4	

SUMMARY INCIDENCE TABLE

09001
Recovery Sacrifice
Female Rat

	GROUP 0ppm	GROUP 0.1ppm	GROUP 1.0ppm	GROUP 10ppm	GROUP 30ppm	
Nose, Level 1 (NO. EXAMINED)	(10)	(9)	(10)	(10)	(10)	
Transitional/Respiratory						
Epithelium, Hyperplasia						
Transitional/Respiratory						
Epithelium, Inflammation	8	8	9	10	10	
Nose, Level 2 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				6	8	
Olfactory Epithelium,						
Degeneration/Necrosis				5	8	
Transitional/Respiratory						
Epithelium, Hyperplasia						
Transitional/Respiratory						
Epithelium, Inflammation	2			4	5	
Nose, Level 3 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				10	10	
Olfactory Epithelium,						
Degeneration/Necrosis				8	10	
Respiratory Epithelium,						
Inflammation						
Nose, Level 4 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				10	10	
Olfactory Epithelium,						
Degeneration/Necrosis				7	10	
Olfactory Epithelium,						
Inflammation						
Nose, Level 5 (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Nasopharyngeal Duct, Goblet						
Cell, Hypertrophy/Hyperplasia					3	
Olfactory Epithelium, Basal						
Cell, Hyperplasia				6	10	
Olfactory Epithelium,						
Degeneration/Necrosis				2	7	
Nose, Tip (NO. EXAMINED)	(10)	(9)	(10)	(10)	(10)	
Squamous Epithelium,						
Hyperplasia						
Squamous Epithelium,						
Inflammation	8	8	9	10	8	

HISTOPATHOLOGY INCIDENCE TABLES
Recovery Sacrifice

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Male Rat

GROUP
0ppm

ANIMAL	111	112	113	114	115	116	117	118	119	120										
Nose, Level 1			X			X	X	X	X											
Transitional/Respiratory																				
Epithelium, Hyperplasia				1																
Transitional/Respiratory																				
Epithelium, Inflammation	1	1		1	1					2										
Nose, Level 2	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation																				
Nose, Level 3	X	X	X	X		X		X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Respiratory Epithelium,																				
Inflammation					1		1													
Nose, Level 4	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Olfactory Epithelium,																				
Inflammation																				
Nose, Level 5	X	X	X	X	X	X	X	X	X	X										
Nasopharyngeal Duct, Goblet																				
Cell, Hypertrophy/Hyperplasia																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Male Rat

	GROUP 0ppm																			
ANIMAL	111	112	113	114	115	116	117	118	119	120										
Nose, Tip	X			X	X		X	X												
Squamous Epithelium, Hyperplasia										1										
Squamous Epithelium, Inflammation		1	1			2			1	2										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Male Rat

GROUP
0.1ppm

ANIMAL	146	147	148	149	150	151	152	153	154	155
Nose, Level 1			X	X					X	X
Transitional/Respiratory										
Epithelium, Hyperplasia										
Transitional/Respiratory										
Epithelium, Inflammation	1	1			1	1	2	1		
Nose, Level 2	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										
Transitional/Respiratory										
Epithelium, Hyperplasia										
Transitional/Respiratory										
Epithelium, Inflammation										
Nose, Level 3	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										
Respiratory Epithelium,										
Inflammation										
Nose, Level 4	X	X	X	X	X	X	X	X	X	X
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										
Olfactory Epithelium,										
Inflammation										
Nose, Level 5	X	X	X	X	X	X	X	X	X	X
Nasopharyngeal Duct, Goblet										
Cell, Hypertrophy/Hyperplasia										
Olfactory Epithelium, Basal										
Cell, Hyperplasia										
Olfactory Epithelium,										
Degeneration/Necrosis										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Male Rat

GROUP
0.1ppm

ANIMAL	146	147	148	149	150	151	152	153	154	155
Nose, Tip			X		X	X		X	X	X
Squamous Epithelium,										
Hyperplasia										
Squamous Epithelium,										
Inflammation	2	1		1			1			

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Male Rat

	GROUP 1.0ppm											GROUP 10ppm								
ANIMAL	181	182	183	184	185	186	187	188	189	190		216	217	218	220	221	222	223	224	225
Nose, Level 1		X		X	X	X											X			
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation	1		2				1	1	1	1		1	1	1	1	2		1	1	1
Nose, Level 2	X	X	X	X	X	X	X	X	X	X					X					
Olfactory Epithelium, Basal																				
Cell, Hyperplasia												1	1	1		1	1	1	1	1
Olfactory Epithelium,																				
Degeneration/Necrosis														1		1	1	2	2	1
Transitional/Respiratory																				
Epithelium, Hyperplasia														1						
Transitional/Respiratory																				
Epithelium, Inflammation																				
Nose, Level 3	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia														1	1	1	1	1	1	1
Olfactory Epithelium,																				
Degeneration/Necrosis												1	1	1	1	1	1	1	1	1
Respiratory Epithelium,																				
Inflammation																				
Nose, Level 4	X	X	X	X	X	X	X	X	X	X										X
Olfactory Epithelium, Basal																				
Cell, Hyperplasia												1		1	1	1	1		1	
Olfactory Epithelium,																				
Degeneration/Necrosis												1	1	1	1	1	1	1.	1	
Olfactory Epithelium,																				
Inflammation																				
Nose, Level 5	X	X	X	X	X	X	X	X	X	X		X	X	X		X		X	X	X
Nasopharyngeal Duct, Goblet																				
Cell, Hypertrophy/Hyperplasia																	1			
Olfactory Epithelium, Basal																				
Cell, Hyperplasia															1		1			
Olfactory Epithelium,																				
Degeneration/Necrosis																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Male Rat

	GROUP 1.0ppm											GROUP 10ppm								
ANIMAL	181	182	183	184	185	186	187	188	189	190		216	217	218	220	221	222	223	224	225
Nose, Tip	X			X	X	X	X	X		X				X					X	
Squamous Epithelium, Hyperplasia																				
Squamous Epithelium, Inflammation		1	2						2			1	1		1	1	1	1		1

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Male Rat

	GROUP 30ppm																			
ANIMAL	251	252	253	254	255	256	257	258	259	260										
Nose, Level 1							X			X										
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation	1	2	1	1	1	1		1	1											
Nose, Level 2					X					X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	1	2	3	1		3	3	3	3											
Olfactory Epithelium,																				
Degeneration/Necrosis	1	2	1	1		2	2	2	2											
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation																				
Nose, Level 3																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	1	2	2	2	2	2	2	2	2	2										
Olfactory Epithelium,																				
Degeneration/Necrosis	1	1	1	2	2	2	1	2	3	2										
Respiratory Epithelium,																				
Inflammation																				
Nose, Level 4																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	2	2	2	2	2	2	2	1	1										
Olfactory Epithelium,																				
Degeneration/Necrosis	1	1	1	1	1	2	1	2	2	2										
Olfactory Epithelium,																				
Inflammation								1												
Nose, Level 5					X															
Nasopharyngeal Duct, Goblet																				
Cell, Hypertrophy/Hyperplasia																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	1	1	2		2	2	2	1	1										
Olfactory Epithelium,																				
Degeneration/Necrosis	1	1				1	1	1		1										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Male Rat

GROUP
30ppm

	ANIMAL																			
	251	252	253	254	255	256	257	258	259	260										
Nose, Tip		X	X	X	X		X	X												
Squamous Epithelium,																				
Hyperplasia																				
Squamous Epithelium,																				
Inflammation	1					1			2	1										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Female Rat

	GROUP 0ppm																			
ANIMAL	311	312	313	314	315	316	317	318	319	320										
Nose, Level 1				X		X														
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation	1	1	1		2		2	1	3	1										
Nose, Level 2	X	X	X	X			X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation					1	1														
Nose, Level 3	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Respiratory Epithelium,																				
Inflammation																				
Nose, Level 4	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Olfactory Epithelium,																				
Inflammation																				
Nose, Level 5	X	X	X	X	X	X	X	X	X	X										
Nasopharyngeal Duct, Goblet																				
Cell, Hypertrophy/Hyperplasia																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Female Rat

GROUP
0ppm

ANIMAL	311	312	313	314	315	316	317	318	319	320
Nose, Tip			X	X						
Squamous Epithelium, Hyperplasia										
Squamous Epithelium, Inflammation	1	1			2	1	2	2	3	1

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Female Rat

GROUP
0.1ppm

	ANIMAL																			
	346	347	348	349	350	351	352	353	354	355										
Nose, Level 1							N			X										
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation	1	2	1	1	1	2		2	2											
Nose, Level 2	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation																				
Nose, Level 3	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Respiratory Epithelium,																				
Inflammation																				
Nose, Level 4	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Olfactory Epithelium,																				
Inflammation																				
Nose, Level 5	X	X	X	X	X	X	X	X	X	X										
Nasopharyngeal Duct, Goblet																				
Cell, Hypertrophy/Hyperplasia																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Female Rat

	GROUP 0.1ppm																			
ANIMAL	346	347	348	349	350	351	352	353	354	355										
Nose, Tip				X			N													
Squamous Epithelium,																				
Hyperplasia																				
Squamous Epithelium,																				
Inflammation	1	2	1		1	2		1	2	1										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Female Rat

GROUP
1.0ppm

	ANIMAL																			
	381	382	383	384	385	386	387	388	389	390										
Nose, Level 1			X																	
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation	1	2		3	1	1	1	1	2	3										
Nose, Level 2	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation																				
Nose, Level 3	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Respiratory Epithelium,																				
Inflammation																				
Nose, Level 4	X	X	X	X	X	X	X	X	X	X										
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				
Olfactory Epithelium,																				
Inflammation																				
Nose, Level 5	X	X	X	X	X	X	X	X	X	X										
Nasopharyngeal Duct, Goblet																				
Cell, Hypertrophy/Hyperplasia																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia																				
Olfactory Epithelium,																				
Degeneration/Necrosis																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Female Rat

GROUP
1.0ppm

ANIMAL	381	382	383	384	385	386	387	388	389	390
Nose, Tip							X			
Squamous Epithelium,										
Hyperplasia										
Squamous Epithelium,										
Inflammation	1	2	1	2	1	1		1	3	2

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Female Rat

	GROUP 10ppm																			
ANIMAL	416	417	418	419	420	421	422	423	424	425										
Nose, Level 1																				
Transitional/Respiratory Epithelium, Hyperplasia																				
Transitional/Respiratory Epithelium, Inflammation	3	3	2	1	1	1	1	2	2	1										
Nose, Level 2						X	X			X										
Olfactory Epithelium, Basal Cell, Hyperplasia	1	1		1	1			1	1											
Olfactory Epithelium, Degeneration/Necrosis	1			1	1			1	2											
Transitional/Respiratory Epithelium, Hyperplasia																				
Transitional/Respiratory Epithelium, Inflammation	2		2		2			2												
Nose, Level 3																				
Olfactory Epithelium, Basal Cell, Hyperplasia	1	1	1	1	1	1	1	1	1	2										
Olfactory Epithelium, Degeneration/Necrosis		1	1	1	1		1	1	1	1										
Respiratory Epithelium, Inflammation																				
Nose, Level 4																				
Olfactory Epithelium, Basal Cell, Hyperplasia	1	1	1	1	1	1	1	1	1	2										
Olfactory Epithelium, Degeneration/Necrosis		1	1		1		1	1	1	1										
Olfactory Epithelium, Inflammation																				
Nose, Level 5				X	X	X			X											
Nasopharyngeal Duct, Goblet Cell, Hypertrophy/Hyperplasia																				
Olfactory Epithelium, Basal Cell, Hyperplasia	1	1	1				1	1		1										
Olfactory Epithelium, Degeneration/Necrosis		1	1																	

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Female Rat

GROUP
10ppm

	ANIMAL																			
	416	417	418	419	420	421	422	423	424	425										
Nose, Tip																				
Squamous Epithelium,																				
Hyperplasia																				
Squamous Epithelium,																				
Inflammation	3	2	1	1	1	1	1	2	1	1										

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Female Rat

	GROUP 30ppm																			
ANIMAL	451	452	453	454	455	456	457	458	459	460										
Nose, Level 1																				
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation	1	2	1	1	3	1	1	2	2	1										
Nose, Level 2						X														
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	1	2	2	2		3		1	2										
Olfactory Epithelium,																				
Degeneration/Necrosis	2	1	2	2	2		2		1	1										
Transitional/Respiratory																				
Epithelium, Hyperplasia																				
Transitional/Respiratory																				
Epithelium, Inflammation	1			2	2			2	2											
Nose, Level 3																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	1	2	2	3	2	2	2	2	2										
Olfactory Epithelium,																				
Degeneration/Necrosis	2	1	1	1	2	2	2	2	1	2										
Respiratory Epithelium,																				
Inflammation																				
Nose, Level 4																				
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	2	2	2	2	2	2	2	2	2										
Olfactory Epithelium,																				
Degeneration/Necrosis	2	1	1	1	2	2	2	1	2	2										
Olfactory Epithelium,																				
Inflammation																				
Nose, Level 5																				
Nasopharyngeal Duct, Goblet																				
Cell, Hypertrophy/Hyperplasia		1				1	1													
Olfactory Epithelium, Basal																				
Cell, Hyperplasia	2	1	2	2	1	1	2	2	2	1										
Olfactory Epithelium,																				
Degeneration/Necrosis	2	1	1	1	1		1	1												

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

09001
Recovery Sacrifice
Female Rat

GROUP
30ppm

ANIMAL	451	452	453	454	455	456	457	458	459	460
Nose, Tip			X							X
Squamous Epithelium,										
Hyperplasia										
Squamous Epithelium,										
Inflammation	1	1		1	2	1	1	2	1	

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

Dose-response Data and BMD Curves from NTP 2-year Rat Study (NTP, 2000)

NTP Data Available at:
http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr500580/listedreports/tr500/index.html

Female Olfactory Epithelial Hyperplasia (f_oeh_md4) from the 2-year NTP (2000) Study

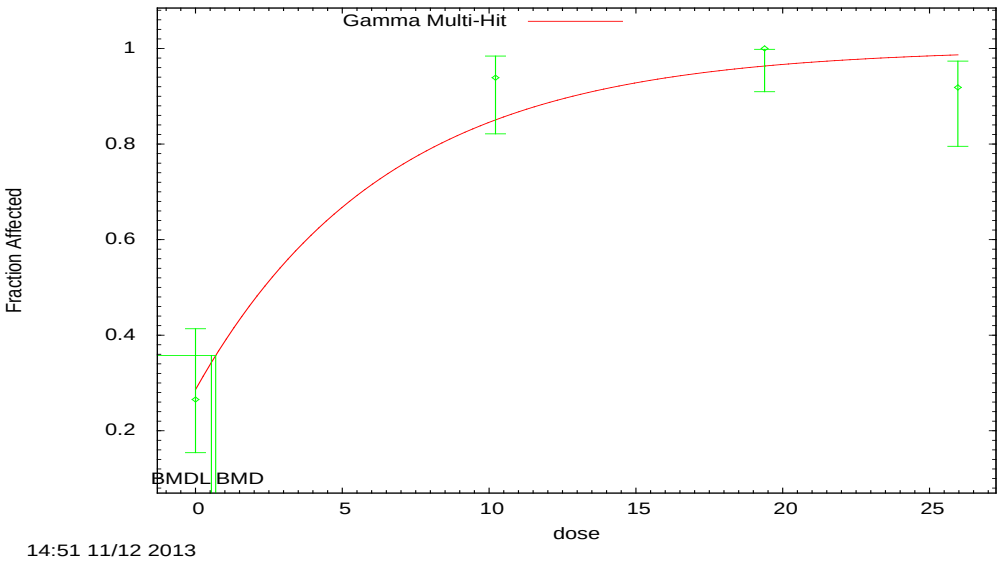
Conc (ppm)	Amt Mtb (nmol/min-g)	Number	Effect
0	0.000	49	0
10	10.219	49	48
30	19.383	49	48
60	25.966	49	43

Male Respiratory Epithelial Hyperplasia (m_reh_md4) from the 2-year NTP (2000) Study

Conc (ppm)	Amt Mtb (nmol/min-g)	Number	Effect
0	0.000	49	3
10	7.123	49	21
30	7.548	48	29
60	8.492	48	29

A: Gamma_f_oed_md4_Gam-BMR10-Restrict

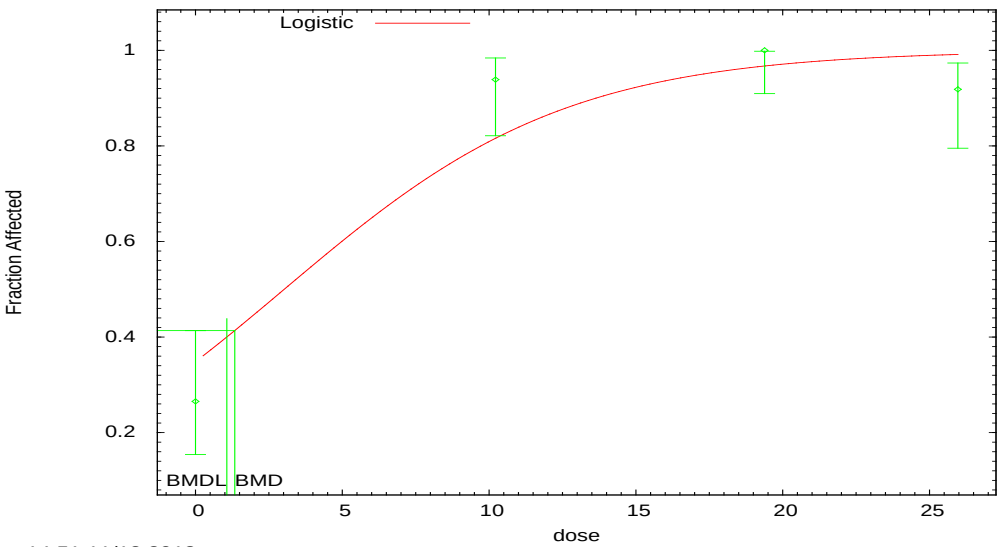
Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:51 11/12 2013

B: Logistic_f_oed_md4_Log-BMR10

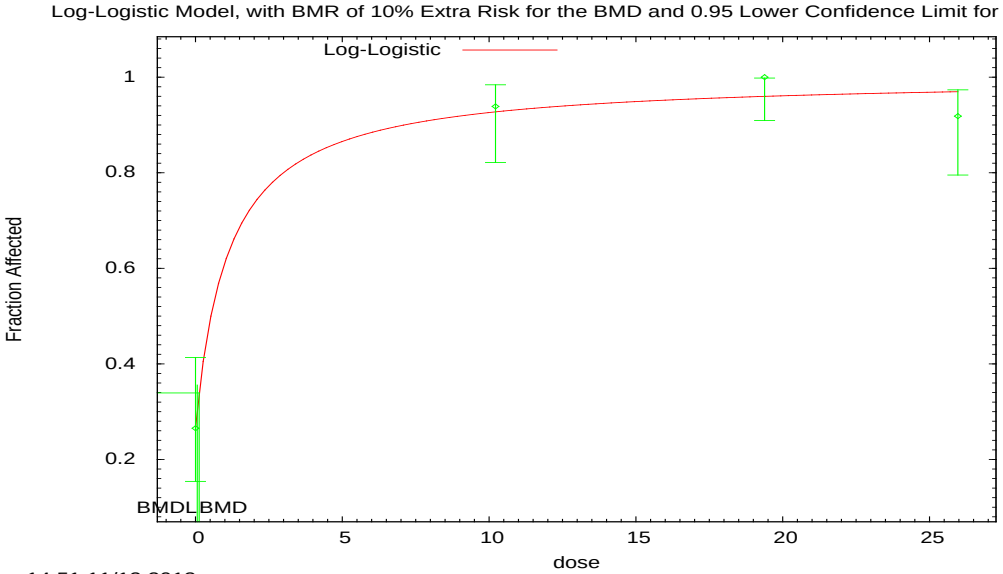
Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:51 11/12 2013

C: LogLogistic_f_oed_md4_Lnl-BMR10-Restrict

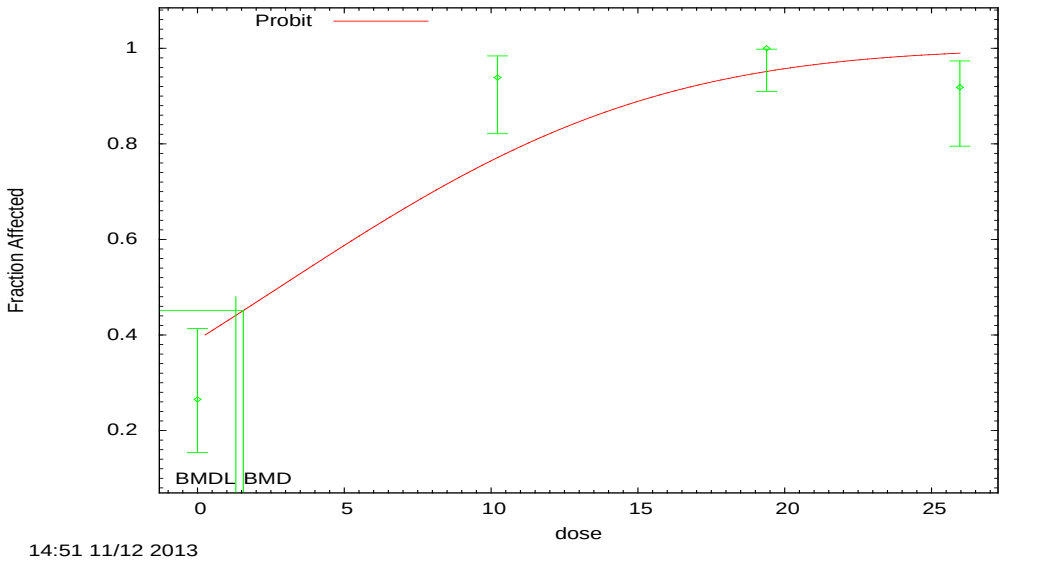
Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



14:51 11/12 2013

D: Probit_f_oed_md4_Pro-BMR10

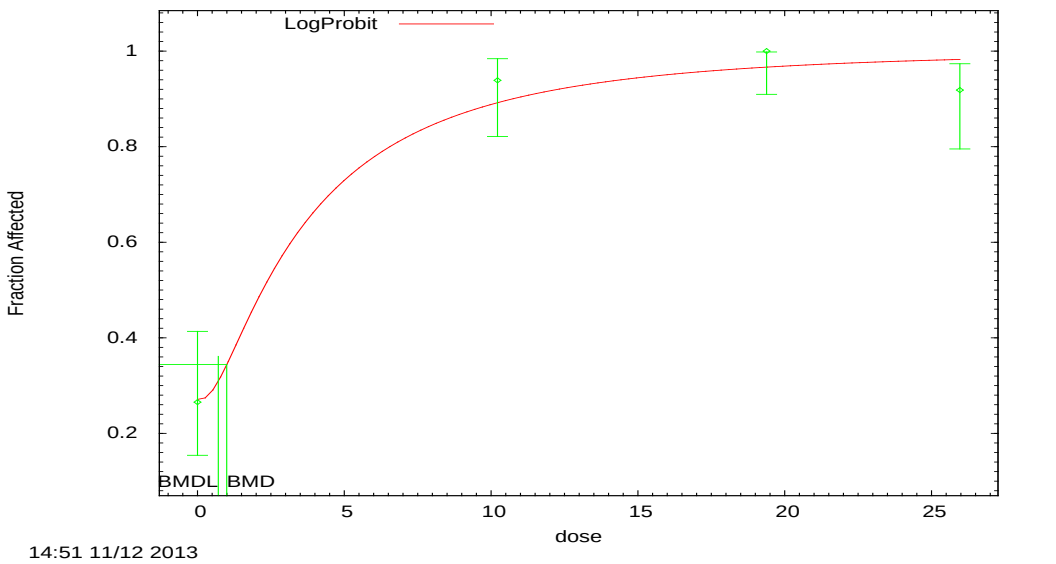
Probit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMI



14:51 11/12 2013

E: LogProbit_f_oed_md4_Lnp-BMR10-Restrict

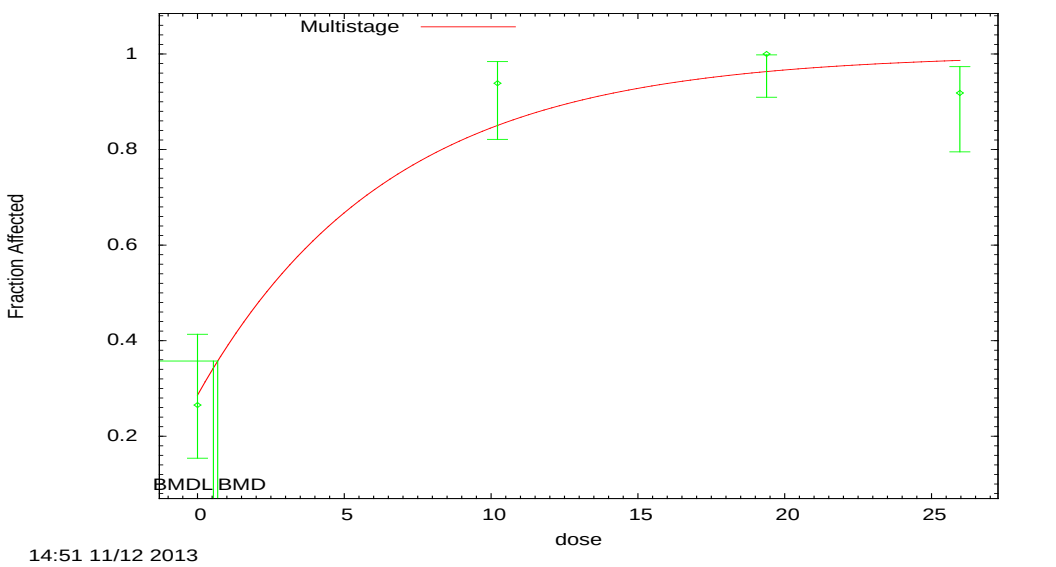
LogProbit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:51 11/12 2013

F: Multistage_f_oed_md4_Mst2-BMR10-Restrict

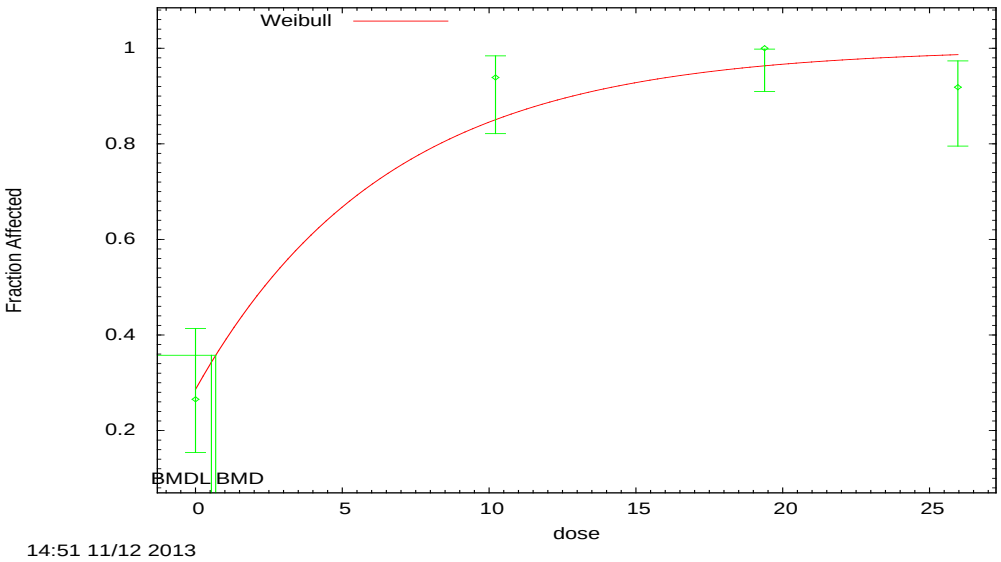
Multistage Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BI



14:51 11/12 2013

G: Weibull_f_oed_md4_Wei-BMR10-Restrict

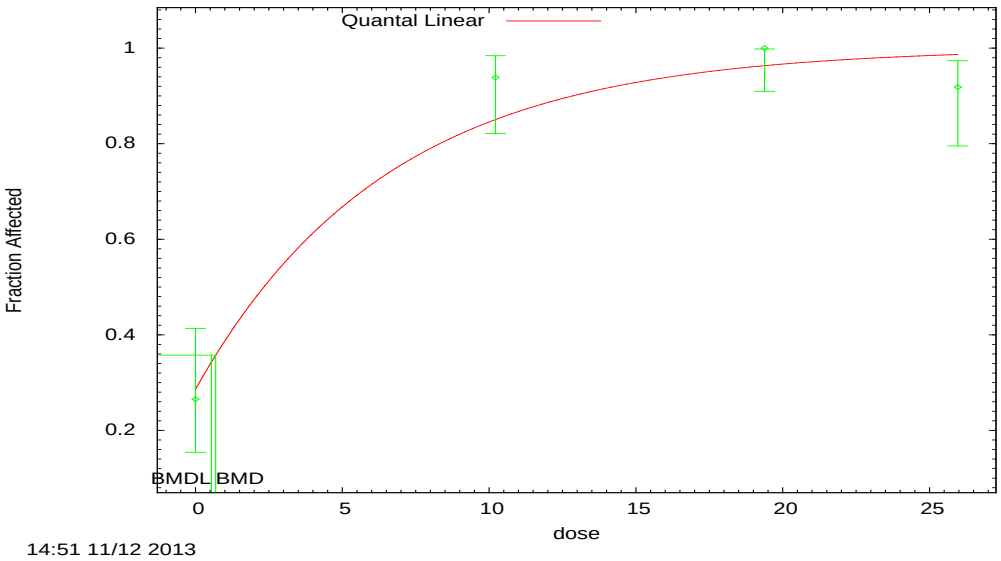
Weibull Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:51 11/12 2013

H: Quantal-Linear_f_oed_md4_Qln-BMR10

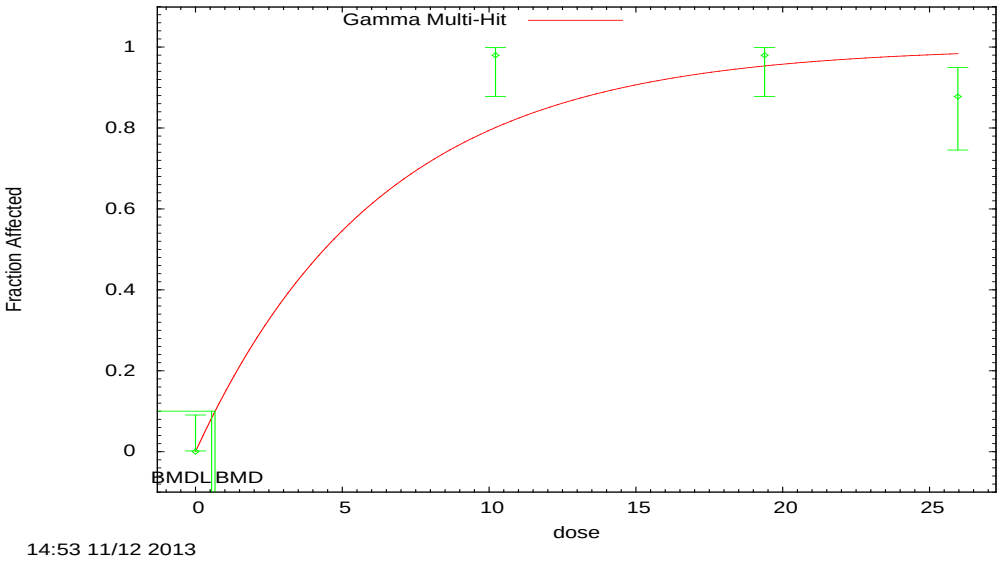
Quantal Linear Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:51 11/12 2013

A: Gamma_f_oeh_md4_Gam-BMR10-Restrict

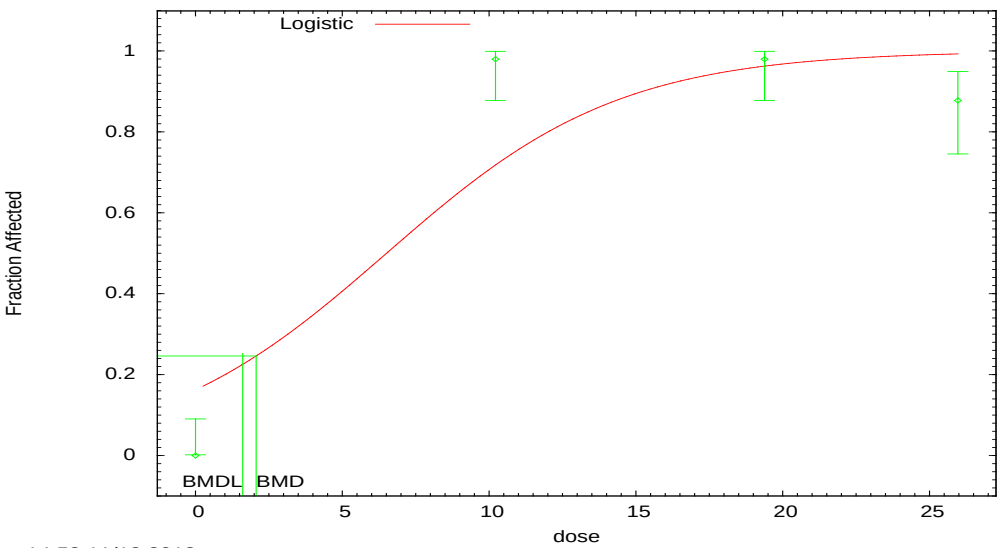
Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:53 11/12 2013

B: Logistic_f_oeh_md4_Log-BMR10

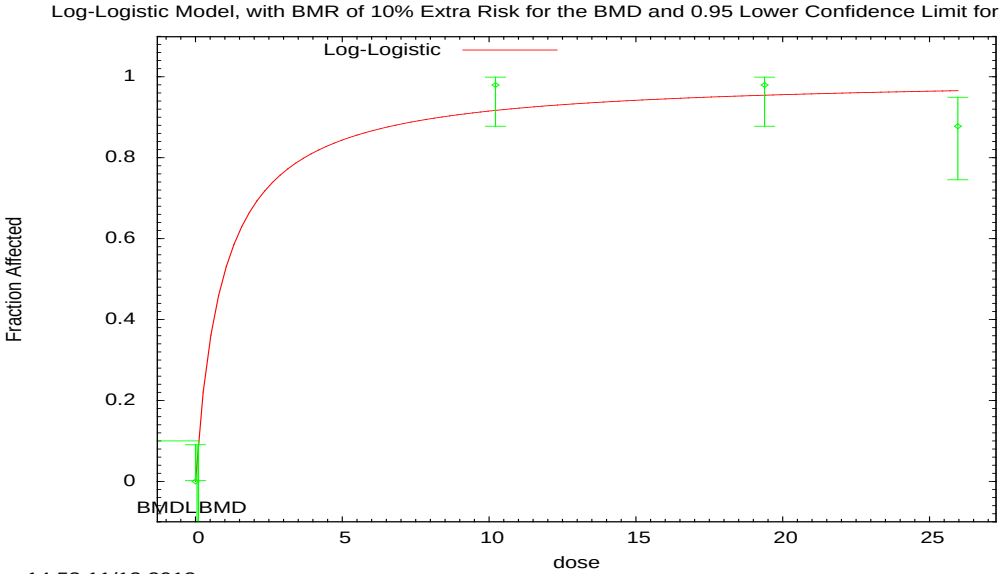
Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:53 11/12 2013

C: LogLogistic_f_oeh_md4_Lnl-BMR10-Restrict

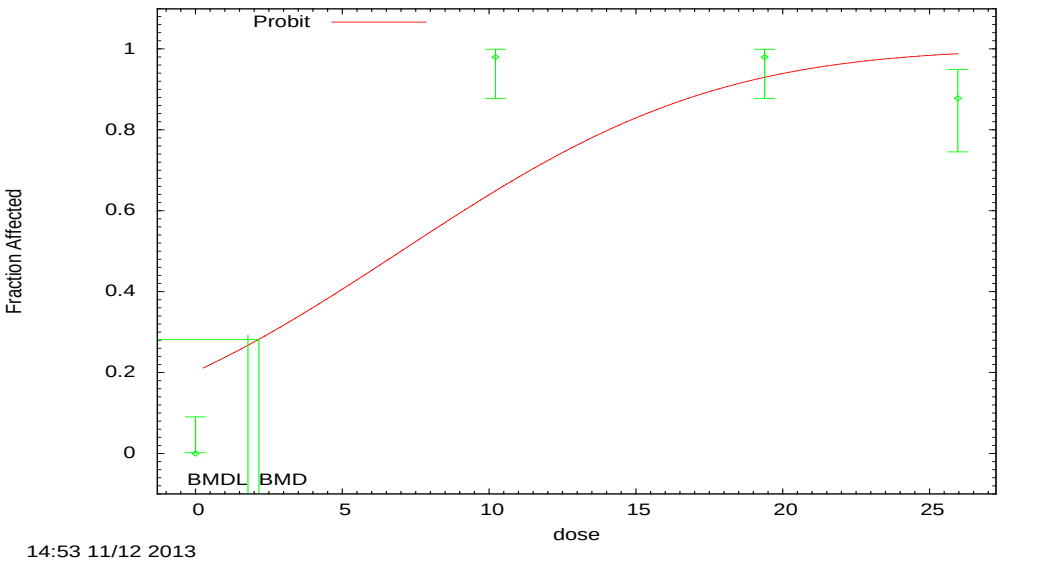
Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



14:53 11/12 2013

D: Probit_f_oeh_md4_Pro-BMR10

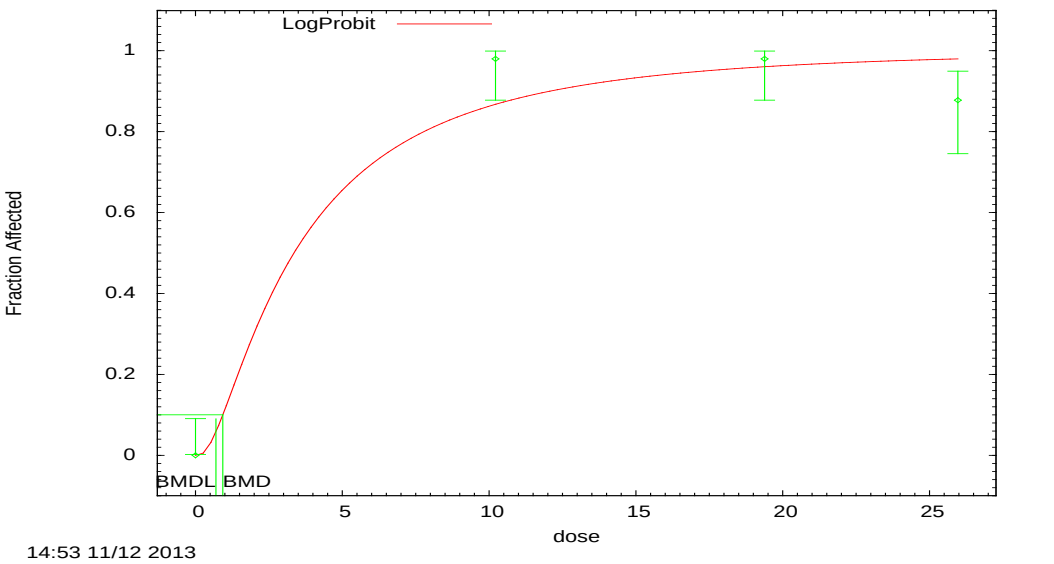
Probit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMI



14:53 11/12 2013

E: LogProbit_f_oeh_md4_Lnp-BMR10-Restrict

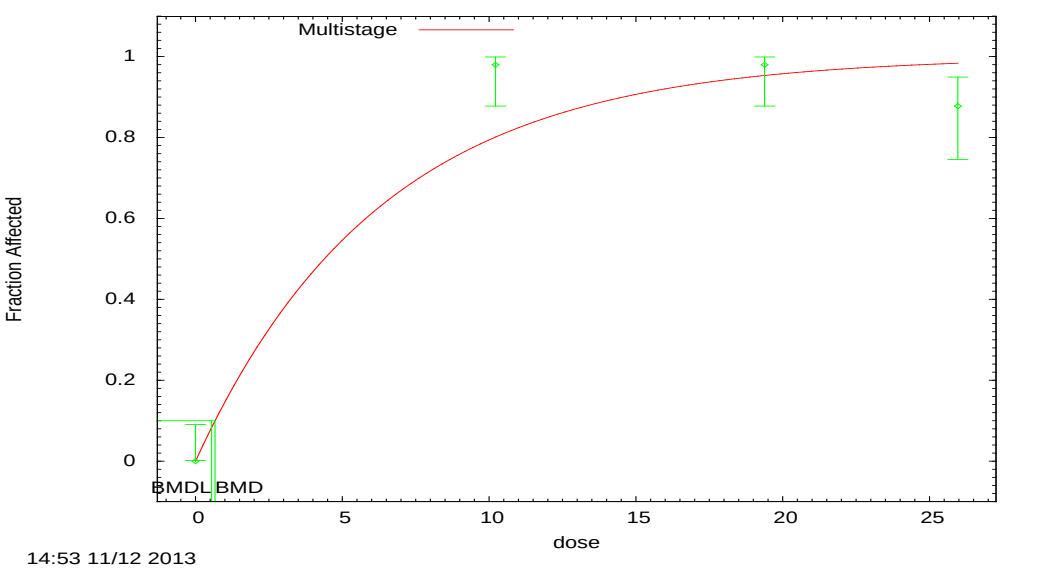
LogProbit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:53 11/12 2013

F: Multistage_f_oeh_md4_Mst2-BMR10-Restrict

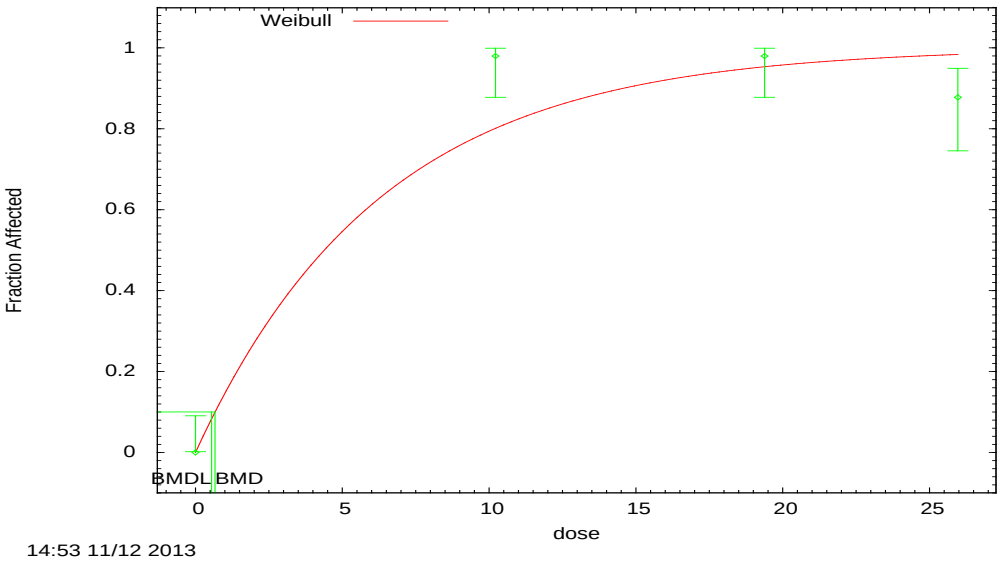
Multistage Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BI



14:53 11/12 2013

G: Weibull_f_oeh_md4_Wei-BMR10-Restrict

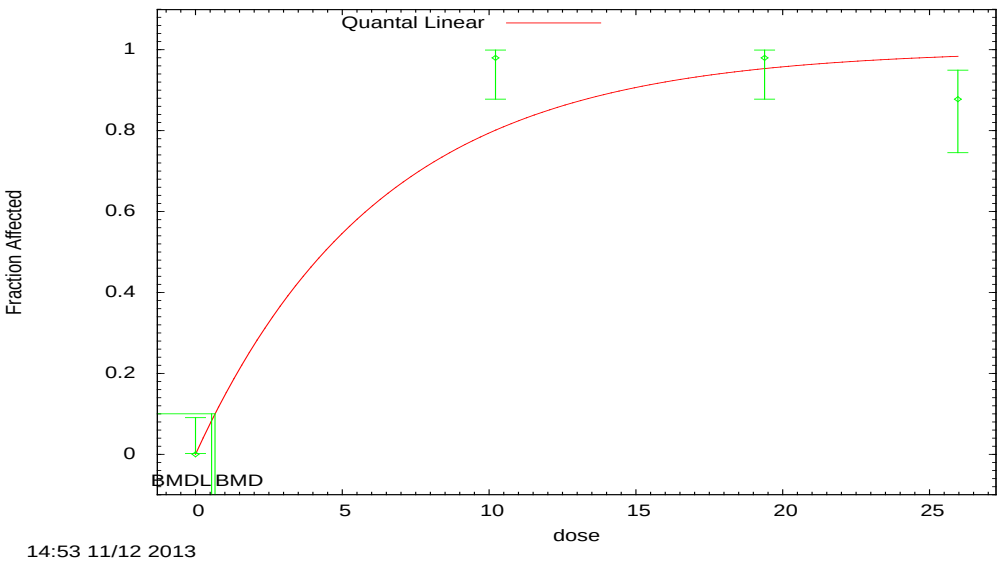
Weibull Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:53 11/12 2013

H: Quantal-Linear_f_oeh_md4_Qln-BMR10

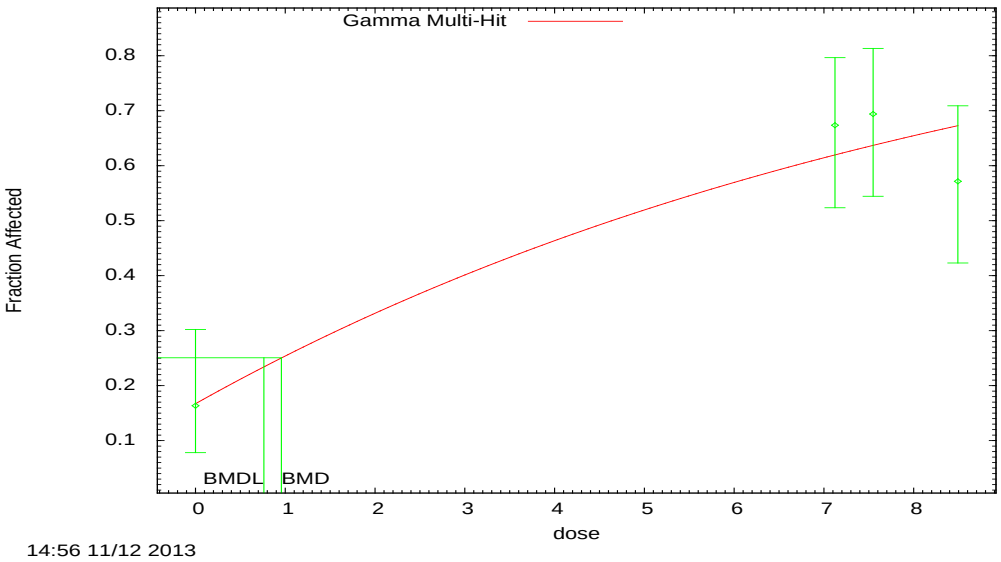
Quantal Linear Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:53 11/12 2013

A: Gamma_f_red_md4_Gam-BMR10-Restrict

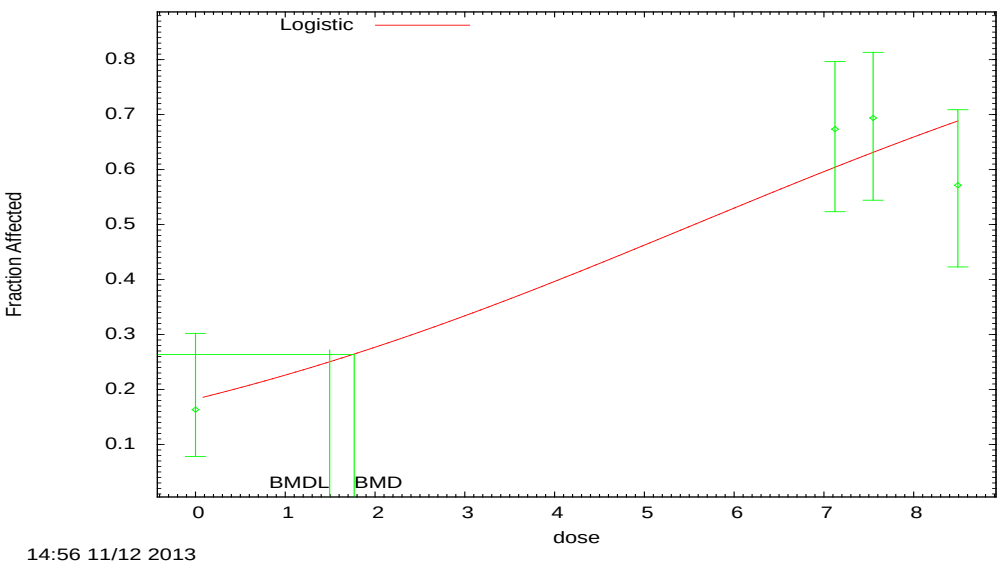
Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:56 11/12 2013

B: Logistic_f_red_md4_Log-BMR10

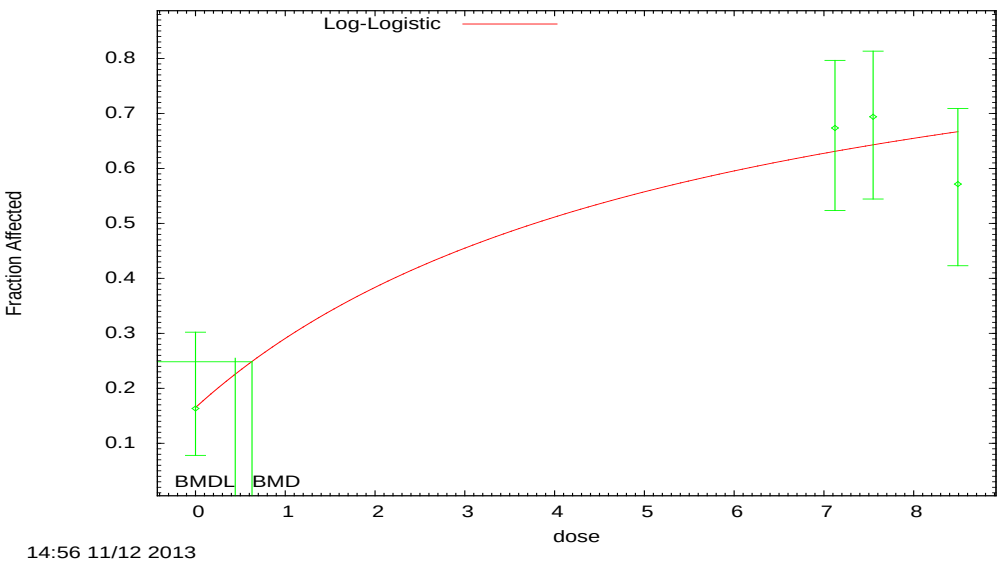
Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:56 11/12 2013

C: LogLogistic_f_red_md4_Lnl-BMR10-Restrict

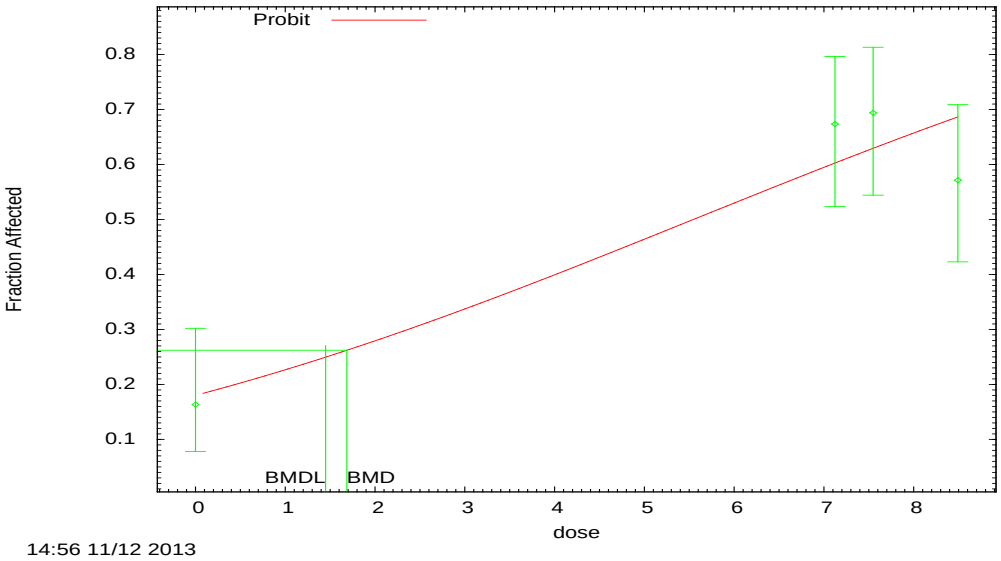
Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



14:56 11/12 2013

D: Probit_f_red_md4_Pro-BMR10

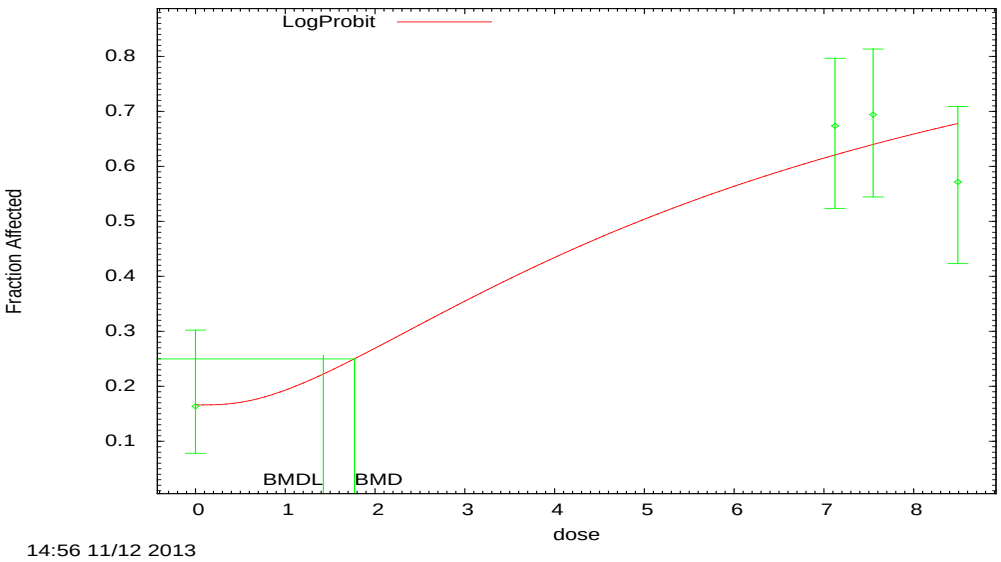
Probit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMI



14:56 11/12 2013

E: LogProbit_f_red_md4_Lnp-BMR10-Restrict

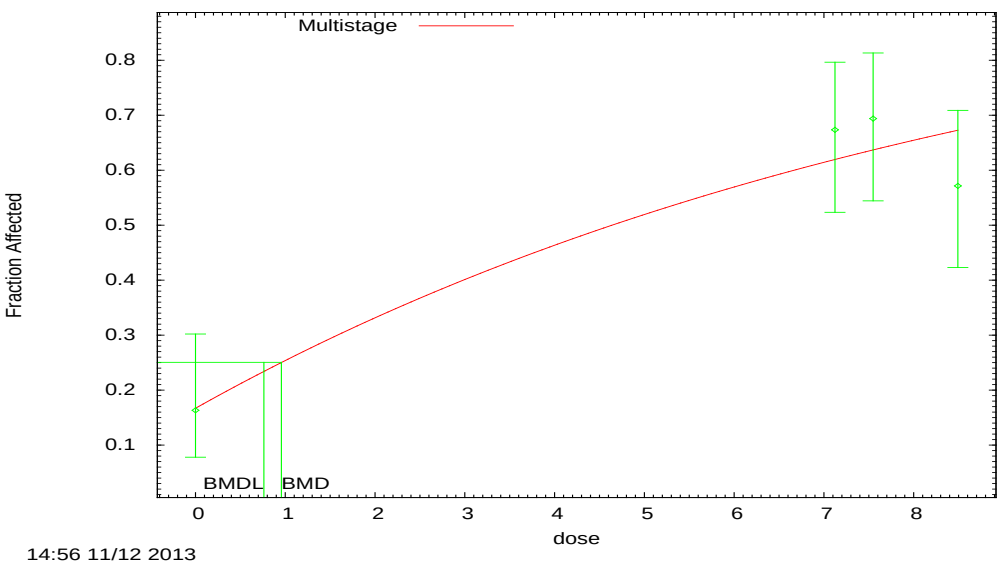
LogProbit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:56 11/12 2013

F: Multistage_f_red_md4_Mst2-BMR10-Restrict

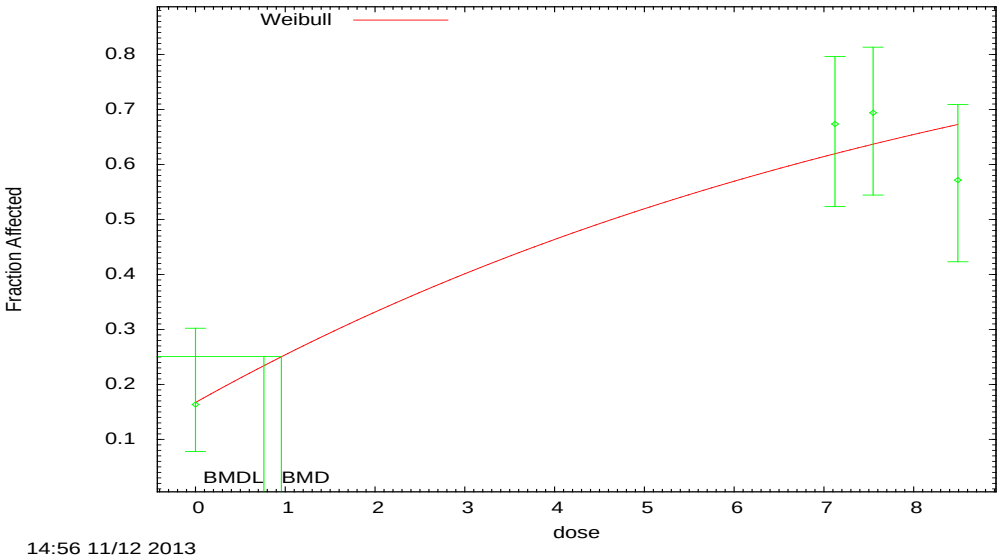
Multistage Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BI



14:56 11/12 2013

G: Weibull_f_red_md4_Wei-BMR10-Restrict

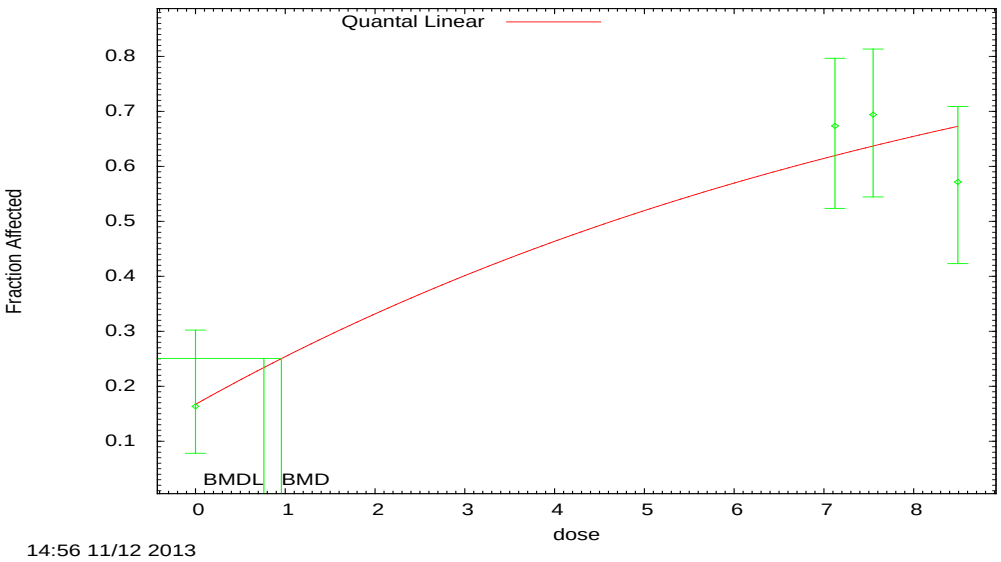
Weibull Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:56 11/12 2013

H: Quantal-Linear_f_red_md4_Qln-BMR10

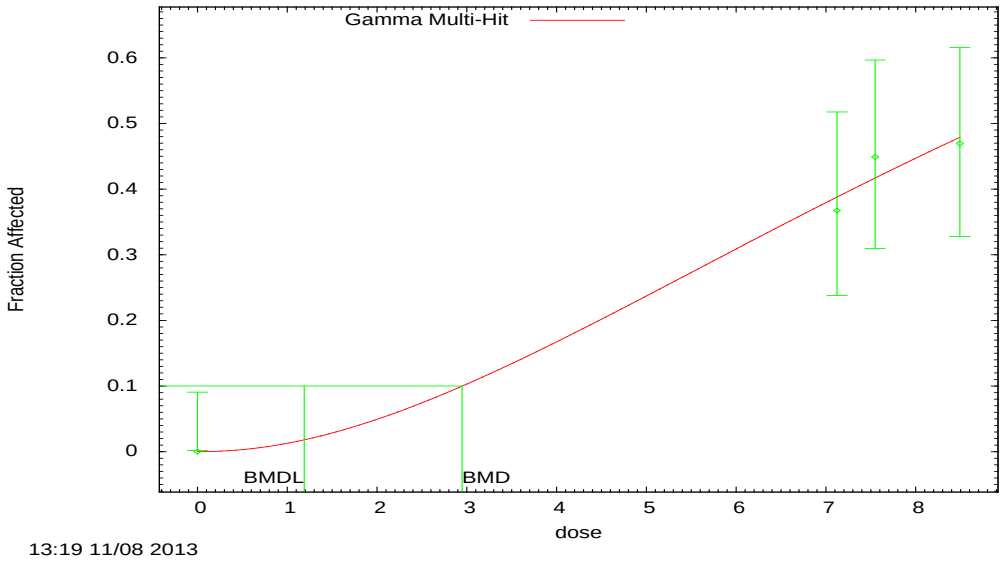
Quantal Linear Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:56 11/12 2013

A: Gamma_f_reh_md4_Gam-BMR10-Restrict

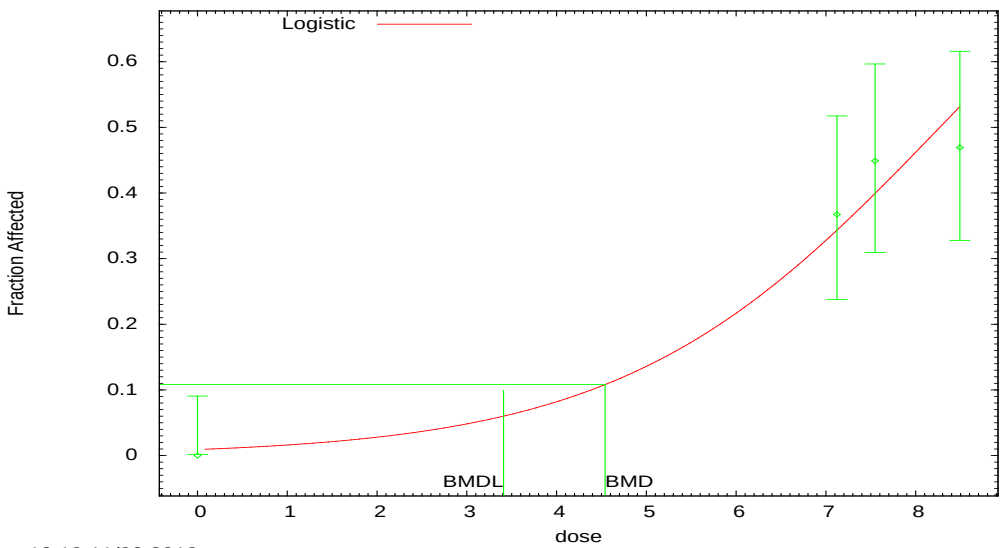
Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



13:19 11/08 2013

B: Logistic_f_reh_md4_Log-BMR10

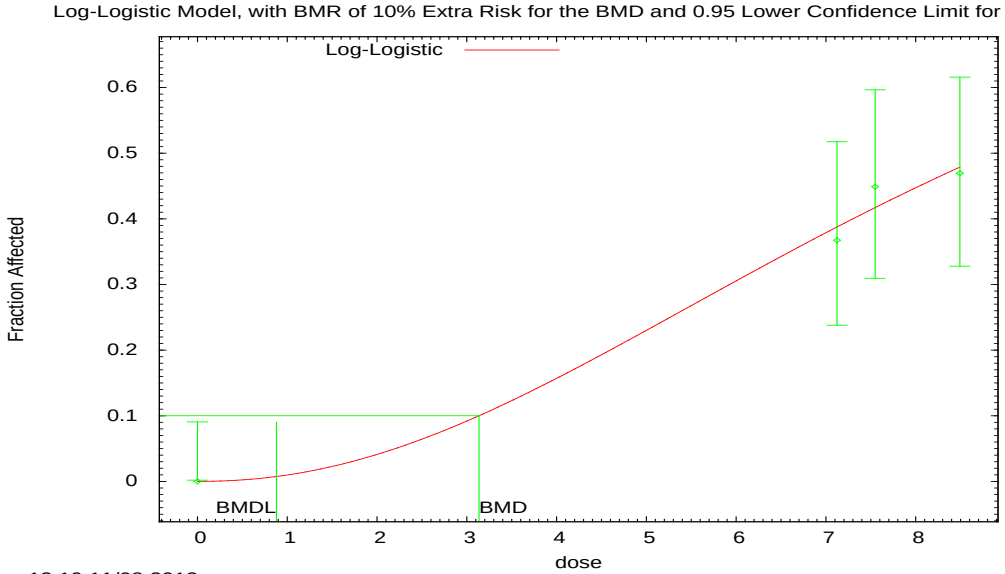
Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



13:19 11/08 2013

C: LogLogistic_f_reh_md4_Lnl-BMR10-Restrict

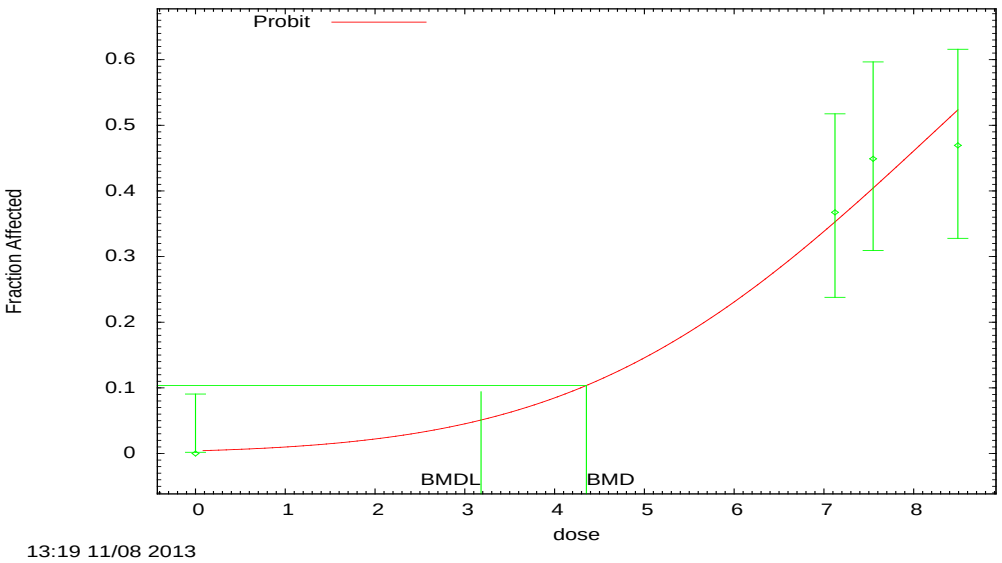
Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



13:19 11/08 2013

D: Probit_f_reh_md4_Pro-BMR10

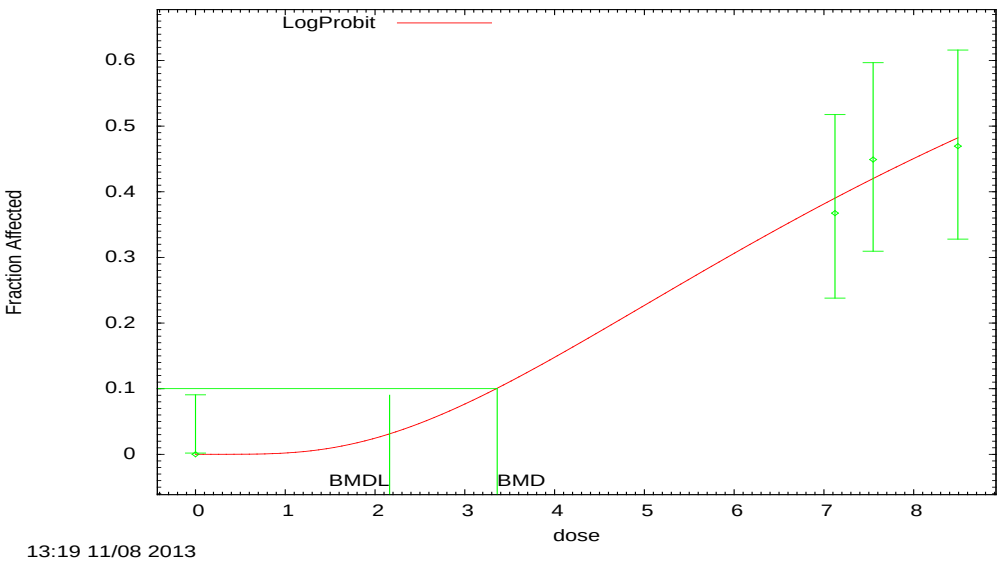
Probit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMI



13:19 11/08 2013

E: LogProbit_f_reh_md4_Lnp-BMR10-Restrict

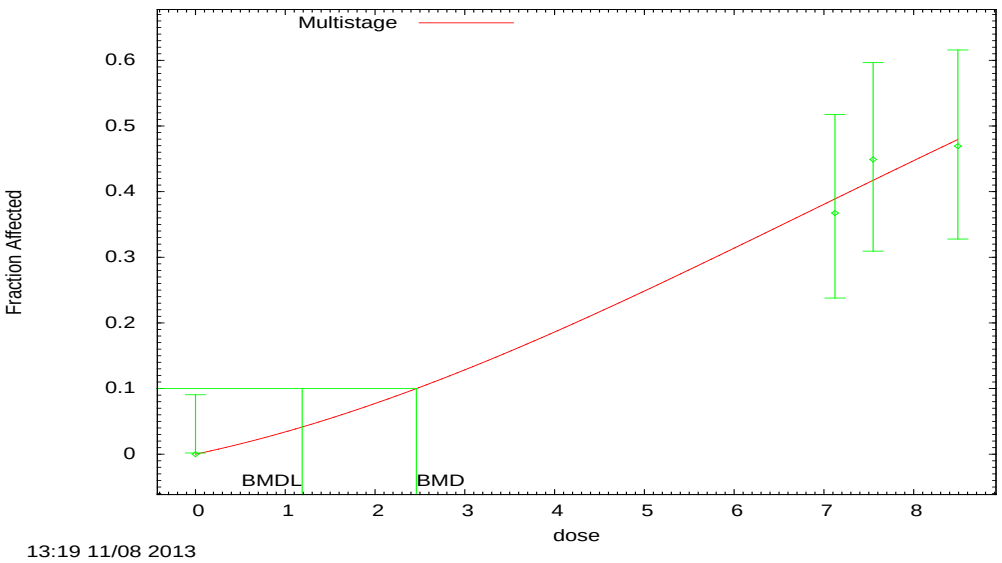
LogProbit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



13:19 11/08 2013

F: Multistage_f_reh_md4_Mst2-BMR10-Restrict

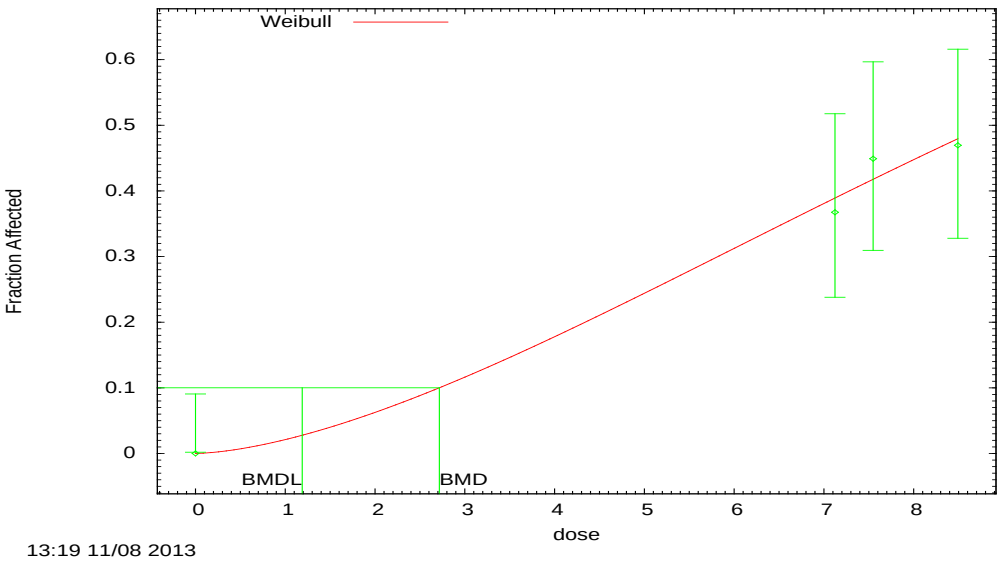
Multistage Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BI



13:19 11/08 2013

G: Weibull_f_reh_md4_Wei-BMR10-Restrict

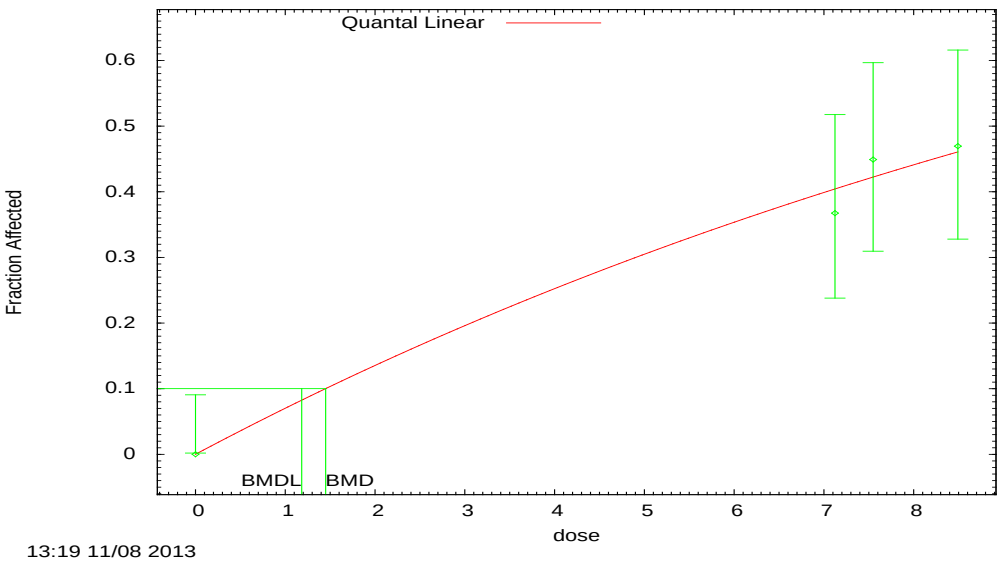
Weibull Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



13:19 11/08 2013

H: Quantal-Linear_f_reh_md4_Qln-BMR10

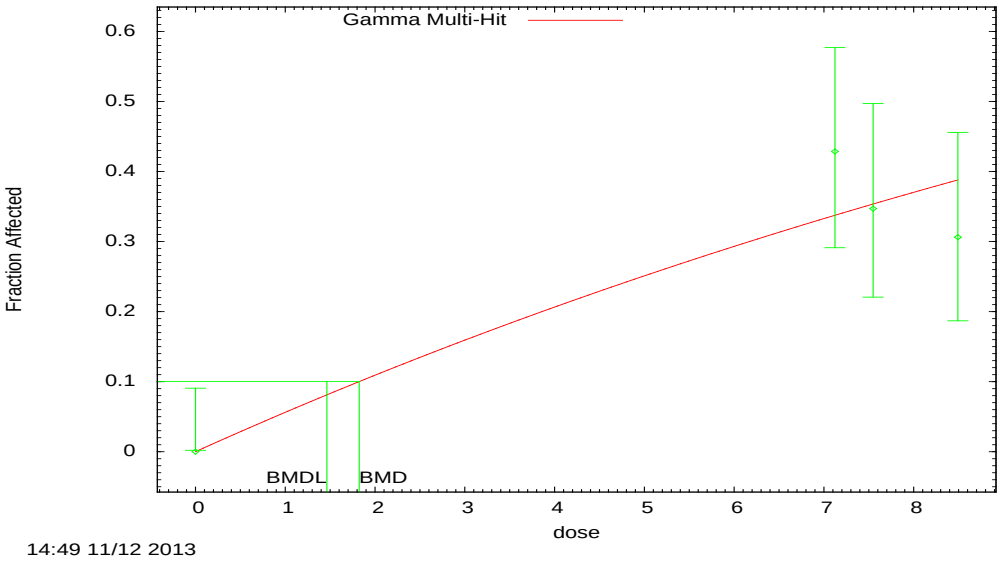
Quantal Linear Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



13:19 11/08 2013

A: Gamma_f_resm_md4_Gam-BMR10-Restrict

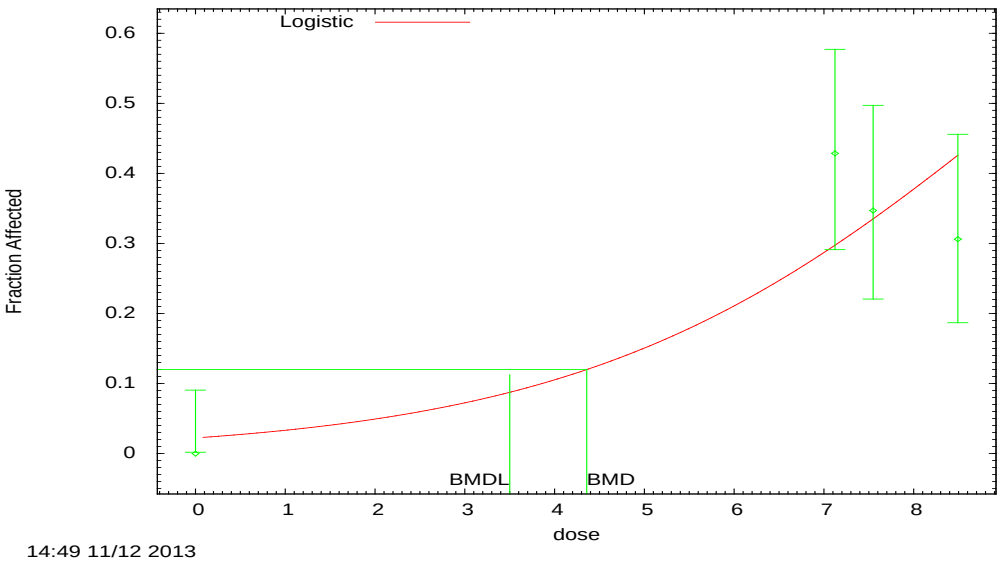
Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:49 11/12 2013

B: Logistic_f_resm_md4_Log-BMR10

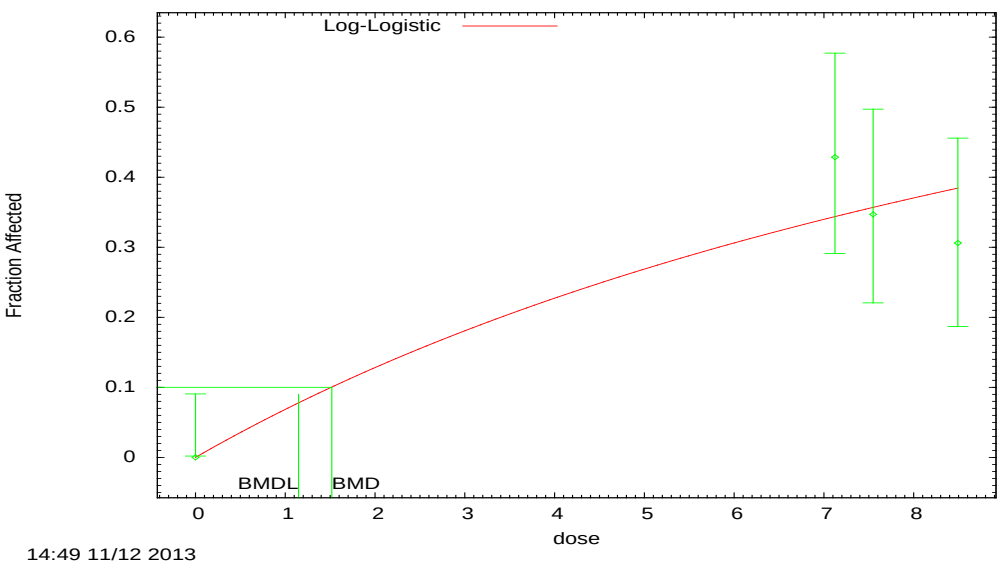
Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:49 11/12 2013

C: LogLogistic_f_resm_md4_Lnl-BMR10-Restrict

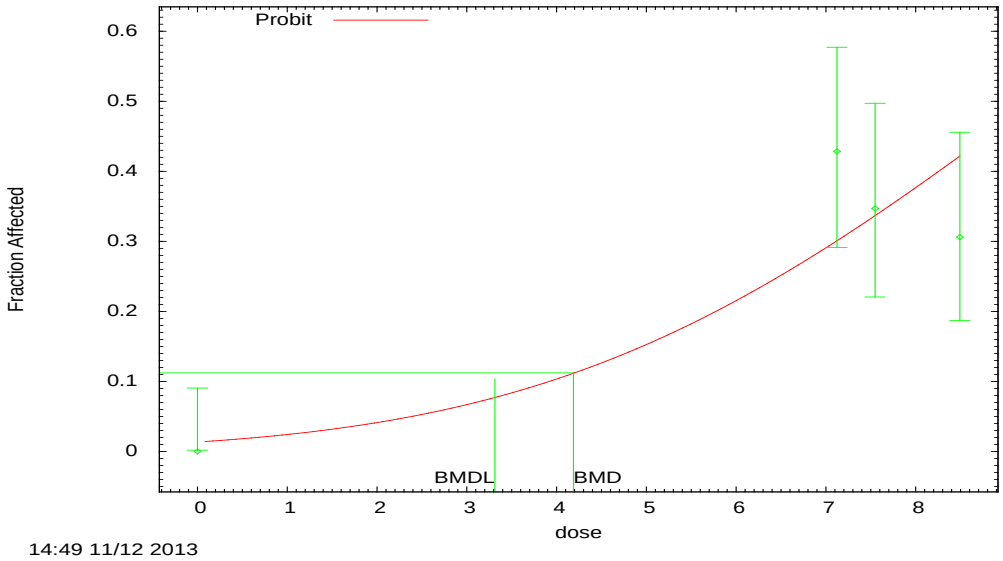
Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



14:49 11/12 2013

D: Probit_f_resm_md4_Pro-BMR10

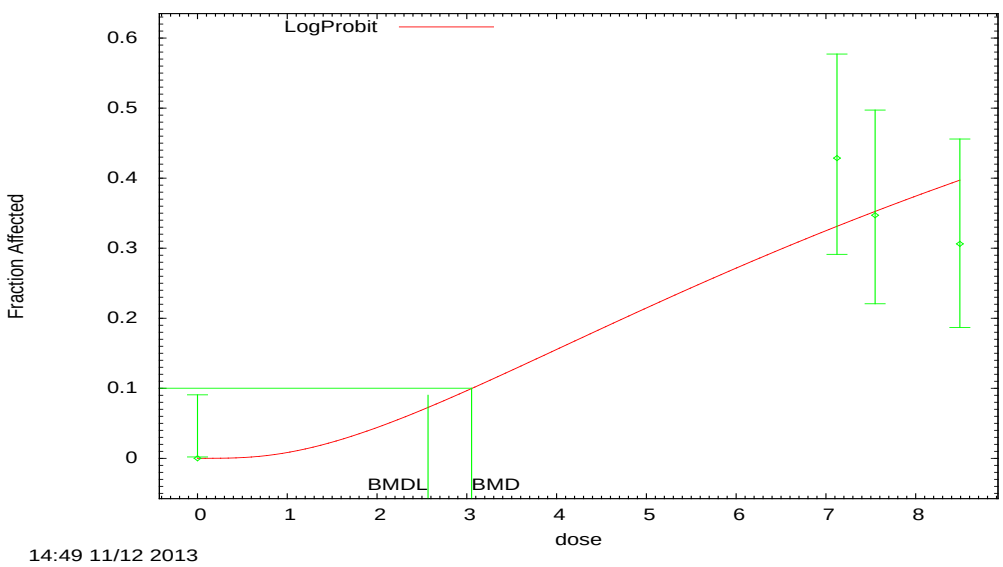
Probit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMI



14:49 11/12 2013

E: LogProbit_f_resm_md4_Lnp-BMR10-Restrict

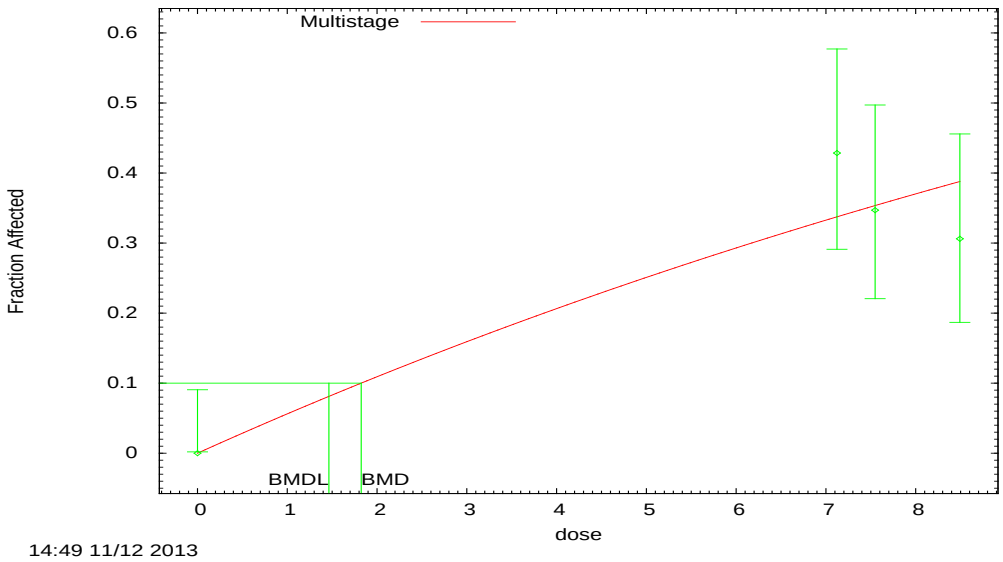
LogProbit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:49 11/12 2013

F: Multistage_f_resm_md4_Mst2-BMR10-Restrict

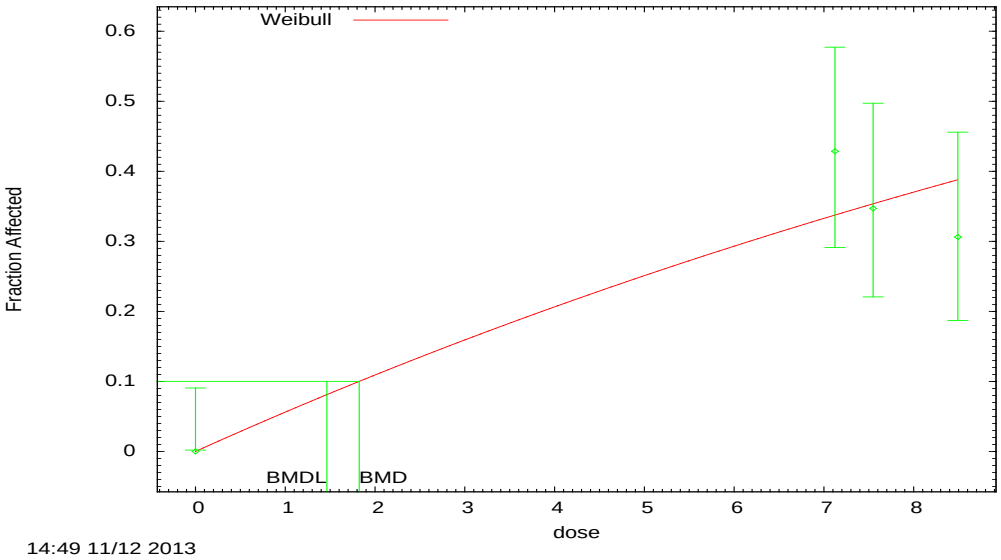
Multistage Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BI



14:49 11/12 2013

G: Weibull_f_resm_md4_Wei-BMR10-Restrict

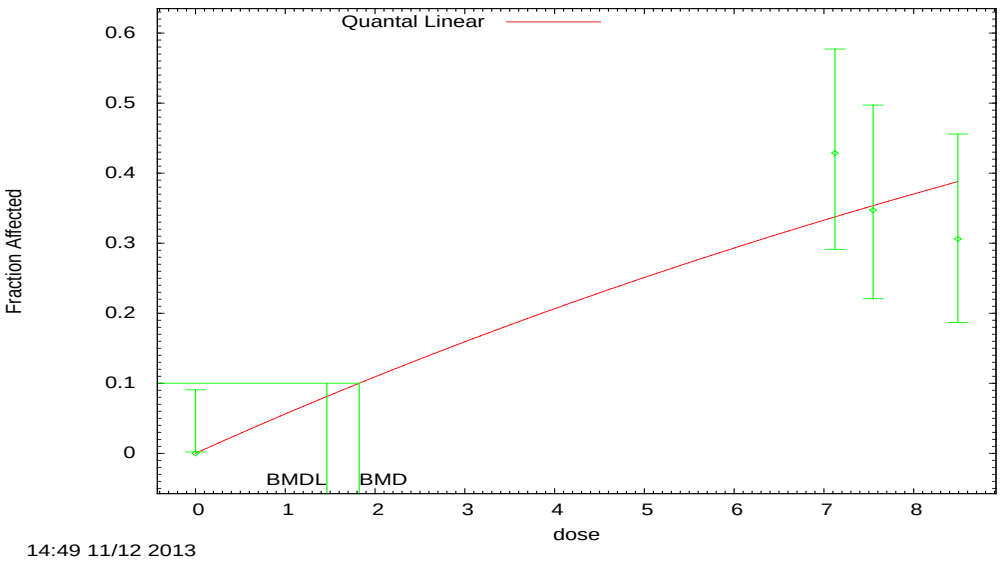
Weibull Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:49 11/12 2013

H: Quantal-Linear_f_resm_md4_Qln-BMR10

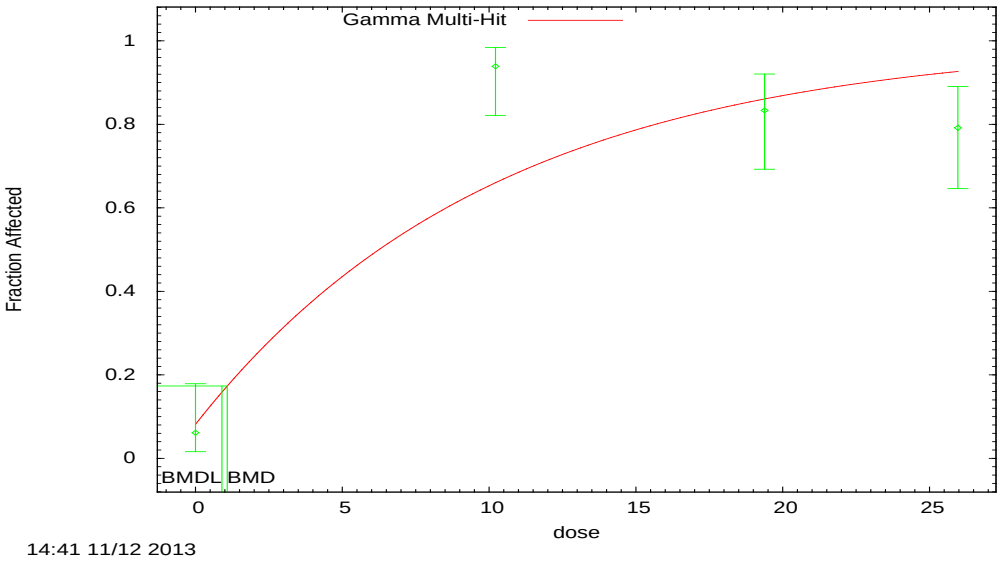
Quantal Linear Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:49 11/12 2013

A: Gamma_m_oed_md4_Gam-BMR10-Restrict

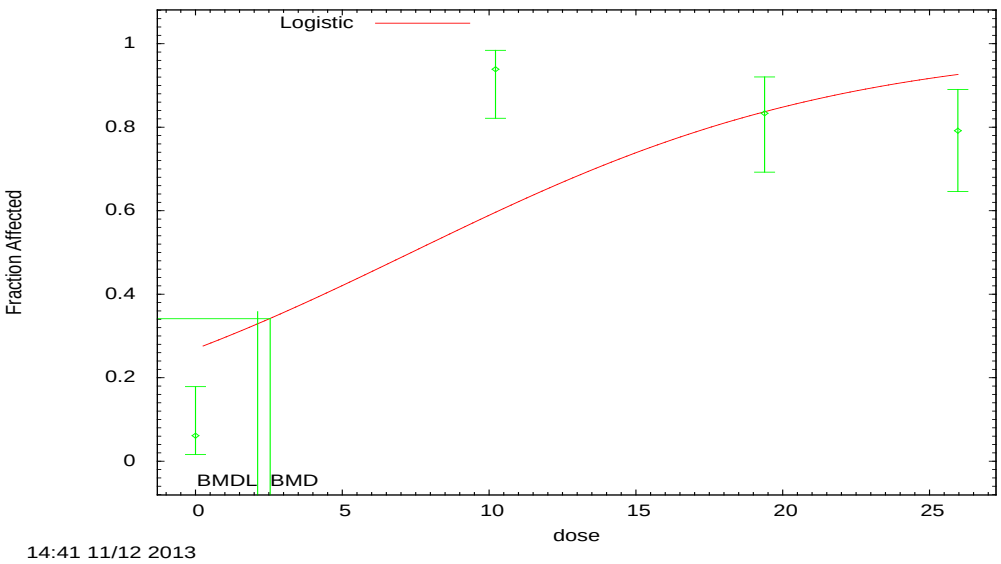
Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:41 11/12 2013

B: Logistic_m_oed_md4_Log-BMR10

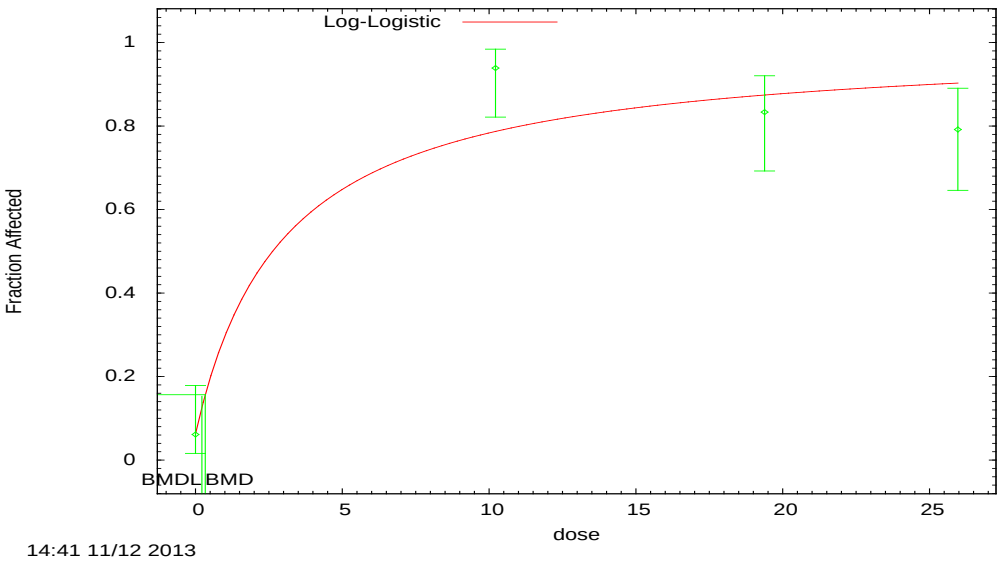
Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:41 11/12 2013

C: LogLogistic_m_oed_md4_Lnl-BMR10-Restrict

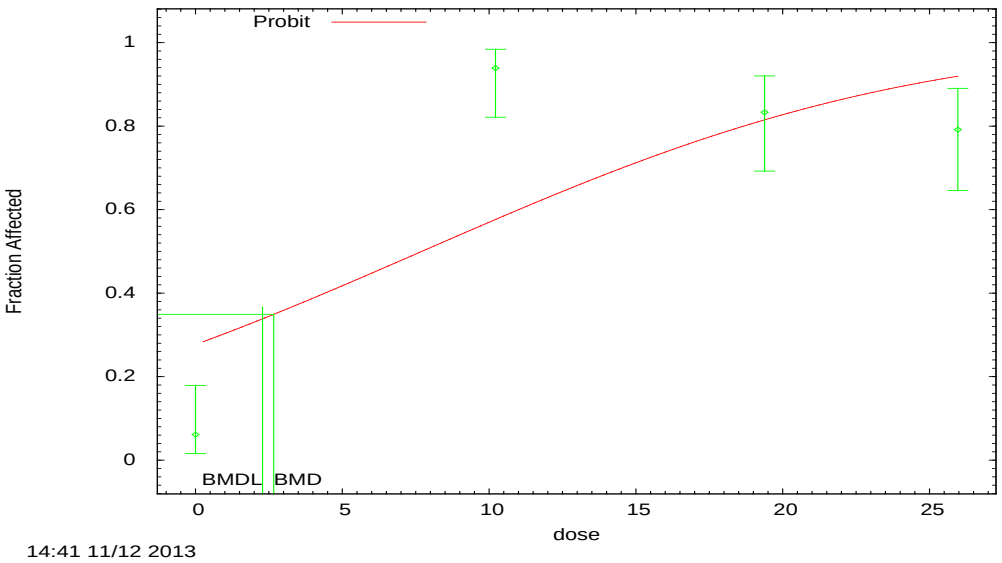
Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



14:41 11/12 2013

D: Probit_m_oed_md4_Pro-BMR10

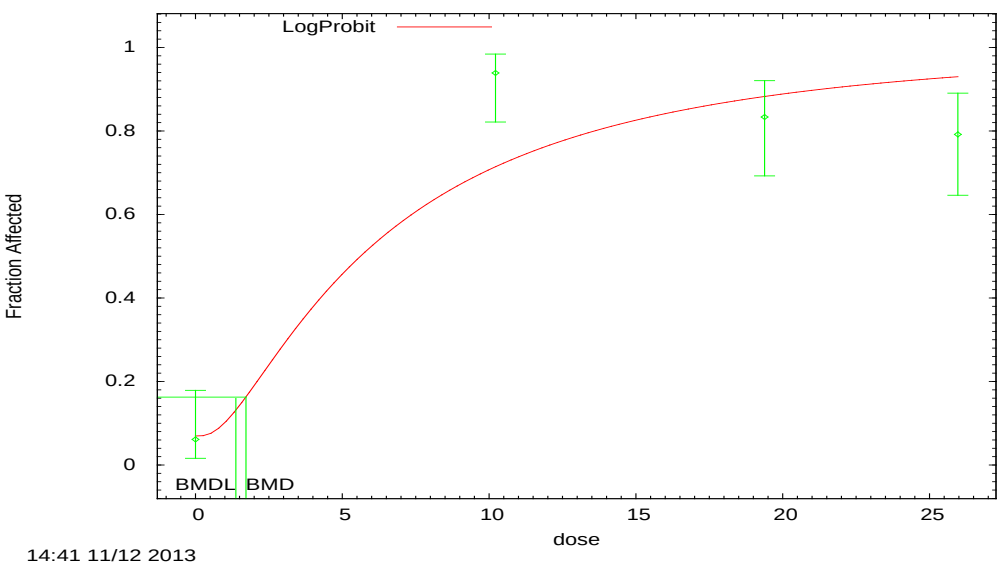
Probit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMI



14:41 11/12 2013

E: LogProbit_m_oed_md4_Lnp-BMR10-Restrict

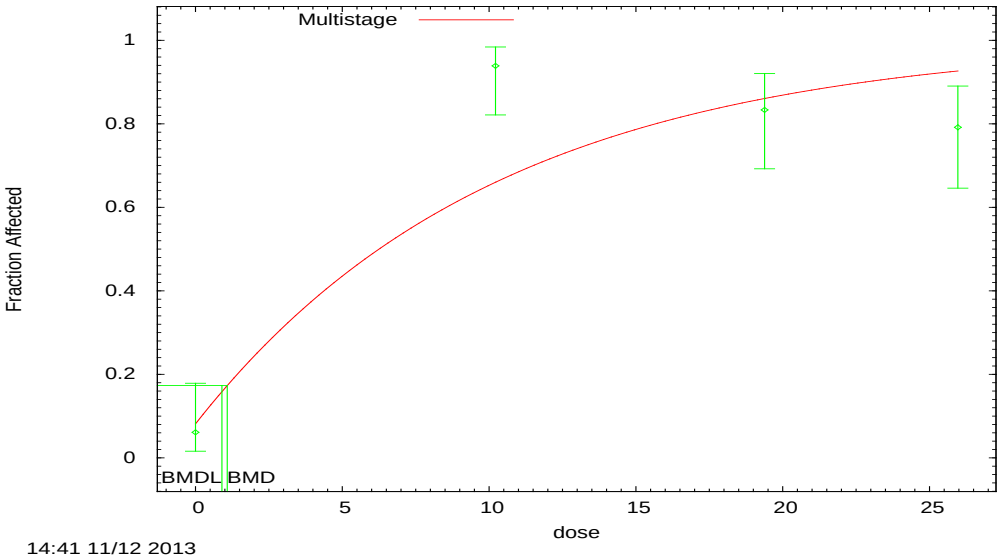
LogProbit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:41 11/12 2013

F: Multistage_m_oed_md4_Mst2-BMR10-Restrict

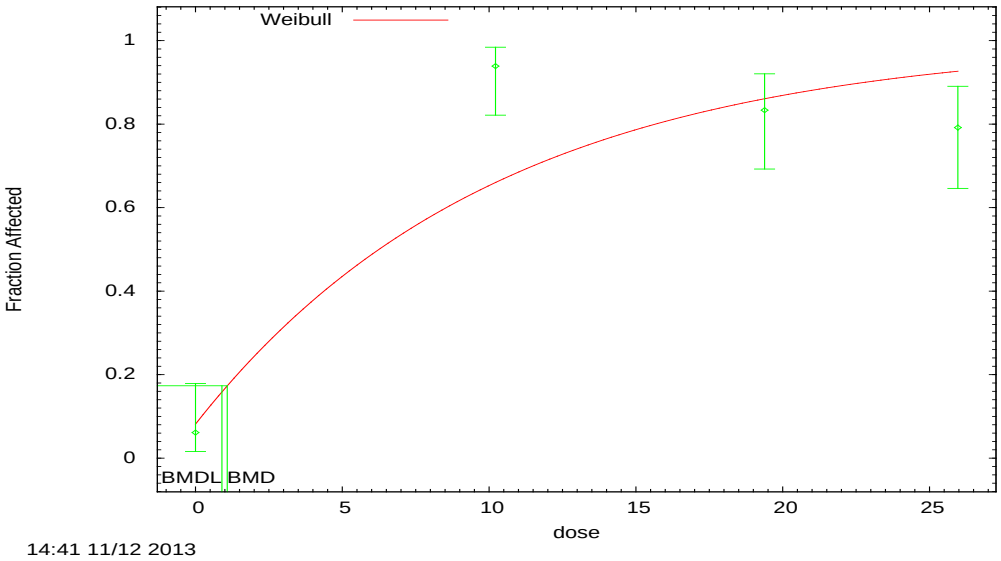
Multistage Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BI



14:41 11/12 2013

G: Weibull_m_oed_md4_Wei-BMR10-Restrict

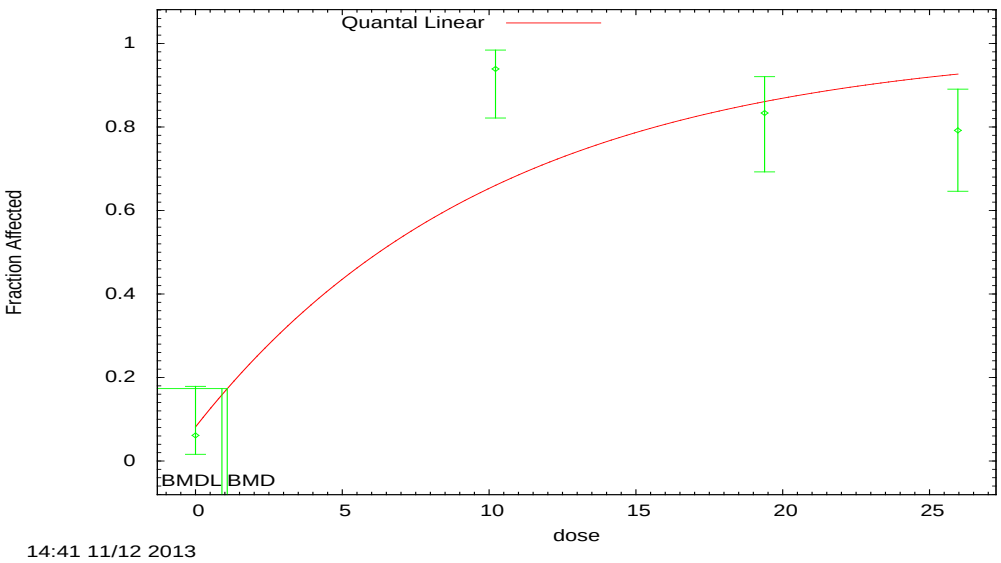
Weibull Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:41 11/12 2013

H: Quantal-Linear_m_oed_md4_Qln-BMR10

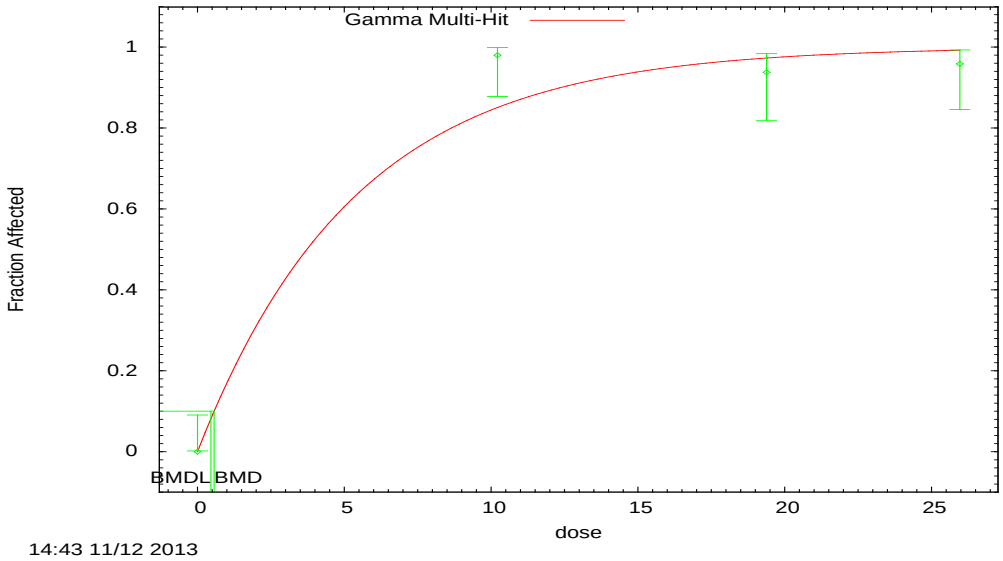
Quantal Linear Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:41 11/12 2013

A: Gamma_m_oeh_md4_Gam-BMR10-Restrict

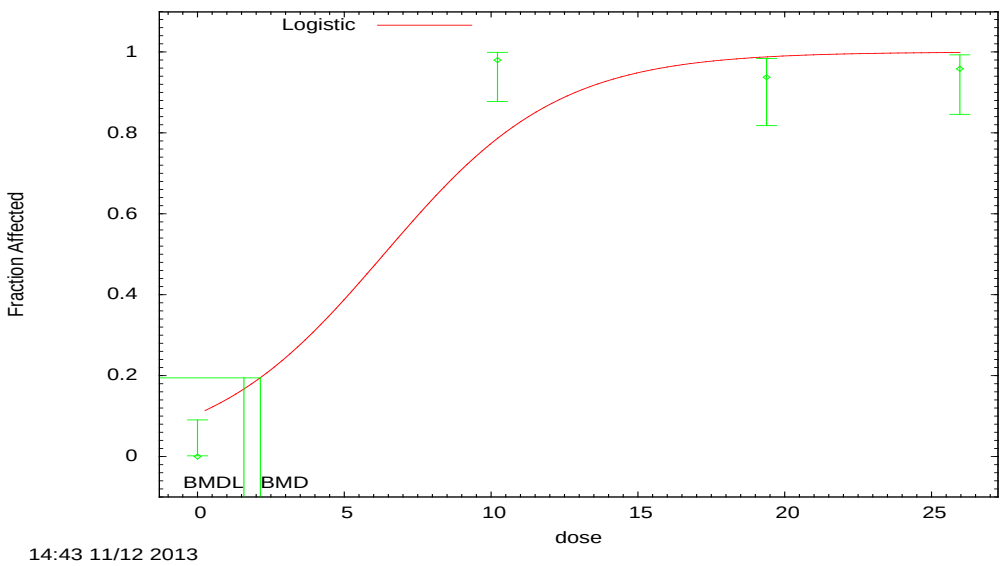
Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:43 11/12 2013

B: Logistic_m_oeh_md4_Log-BMR10

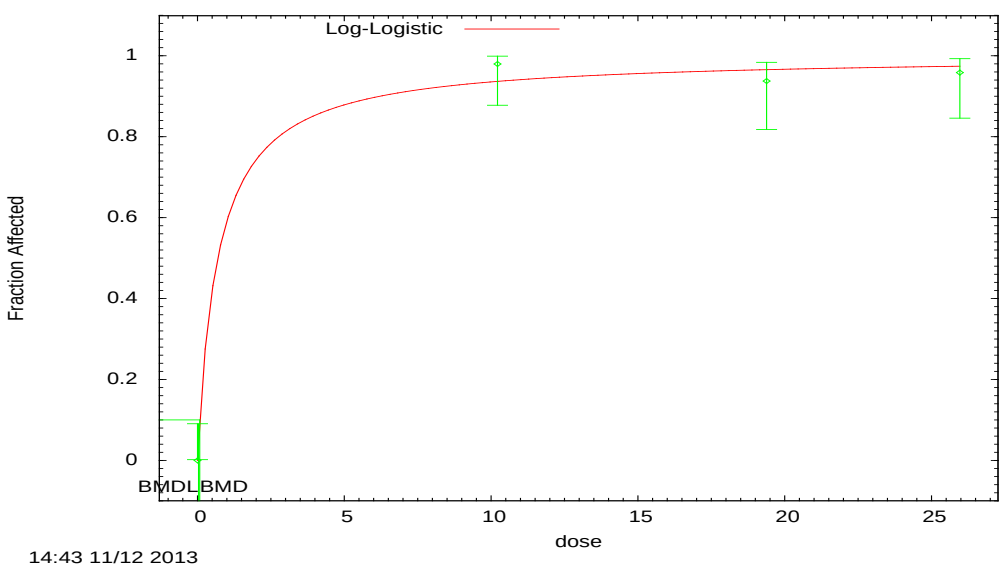
Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:43 11/12 2013

C: LogLogistic_m_oeh_md4_Lnl-BMR10-Restrict

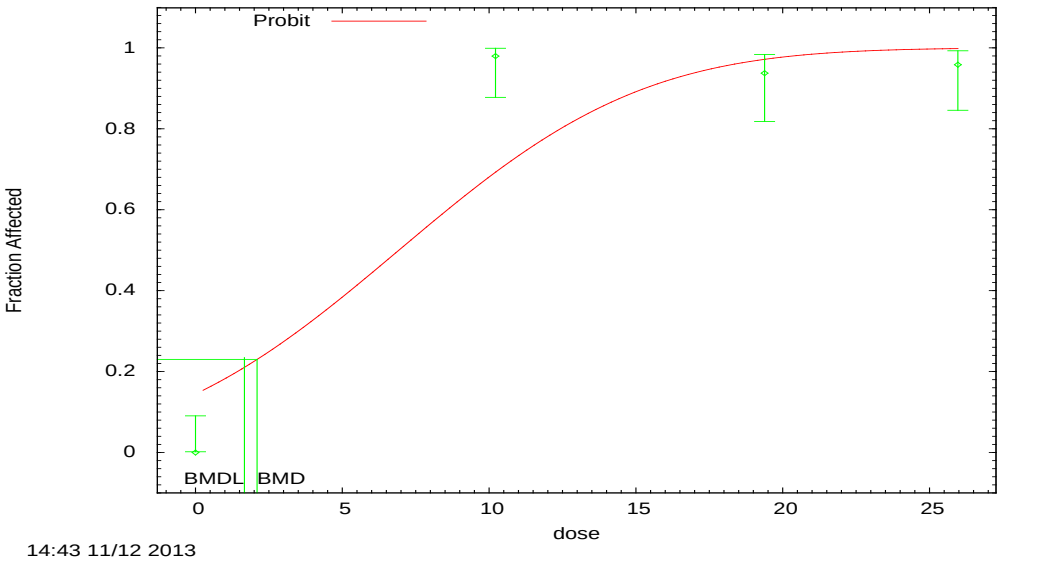
Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



14:43 11/12 2013

D: Probit_m_oeh_md4_Pro-BMR10

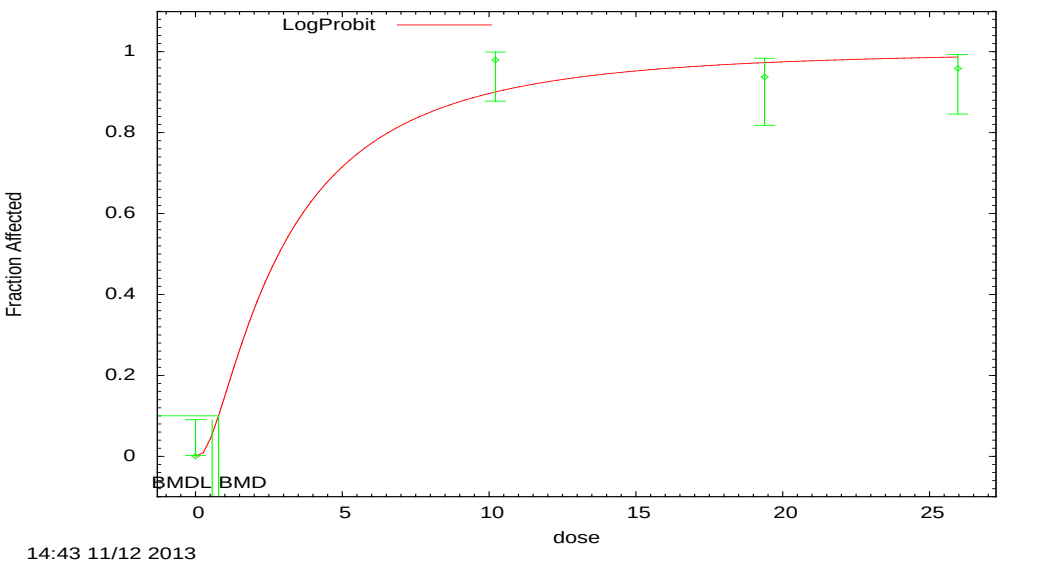
Probit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMI



14:43 11/12 2013

E: LogProbit_m_oeh_md4_Lnp-BMR10-Restrict

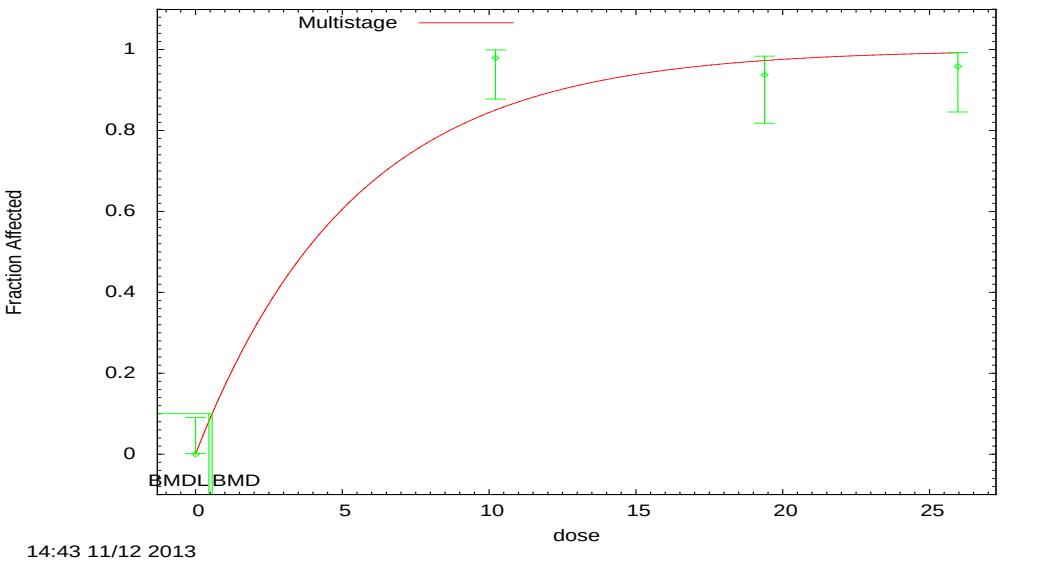
LogProbit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:43 11/12 2013

F: Multistage_m_oeh_md4_Mst2-BMR10-Restrict

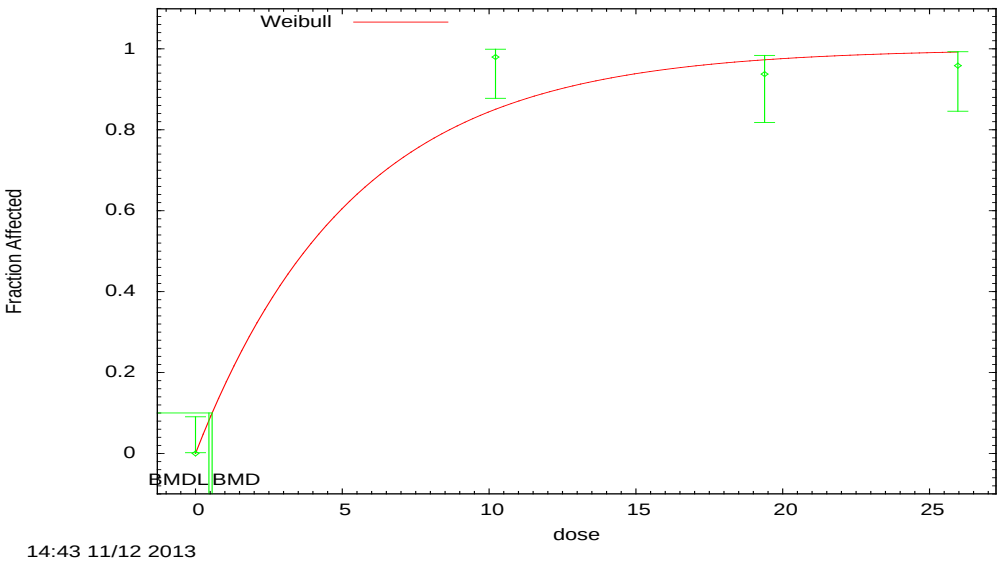
Multistage Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BI



14:43 11/12 2013

G: Weibull_m_oeh_md4_Wei-BMR10-Restrict

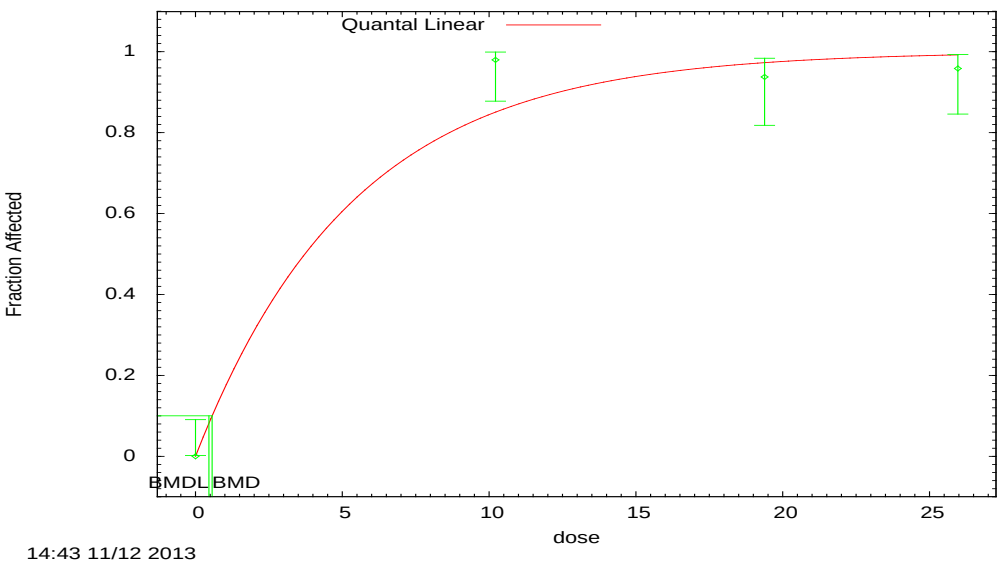
Weibull Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:43 11/12 2013

H: Quantal-Linear_m_oeh_md4_Qln-BMR10

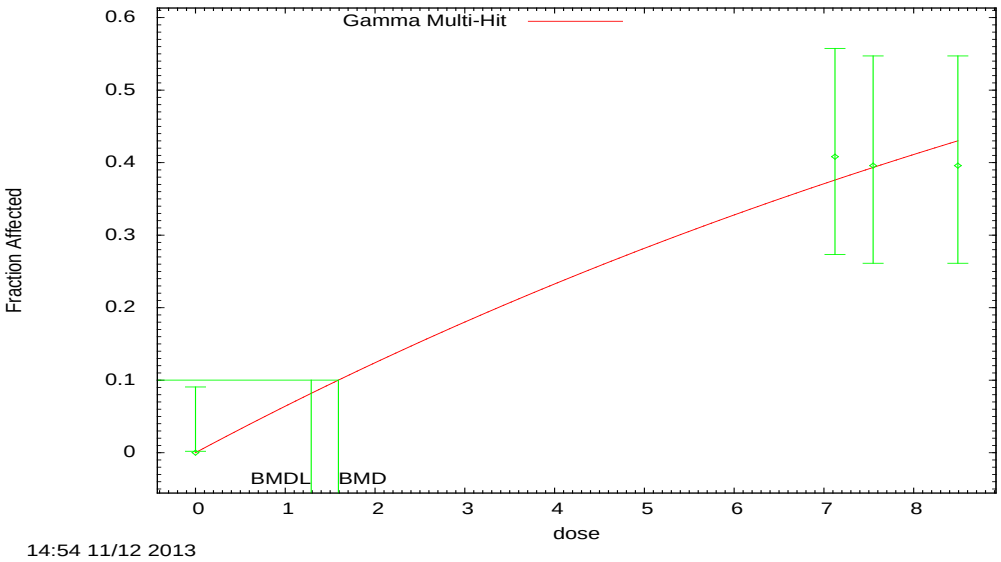
Quantal Linear Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:43 11/12 2013

A: Gamma_m_red_md4_Gam-BMR10-Restrict

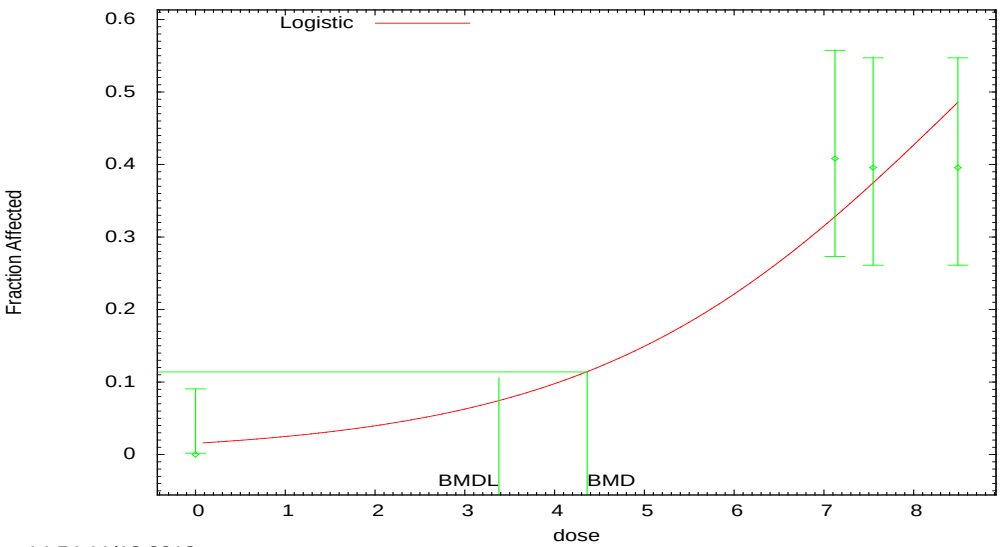
Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:54 11/12 2013

B: Logistic_m_red_md4_Log-BMR10

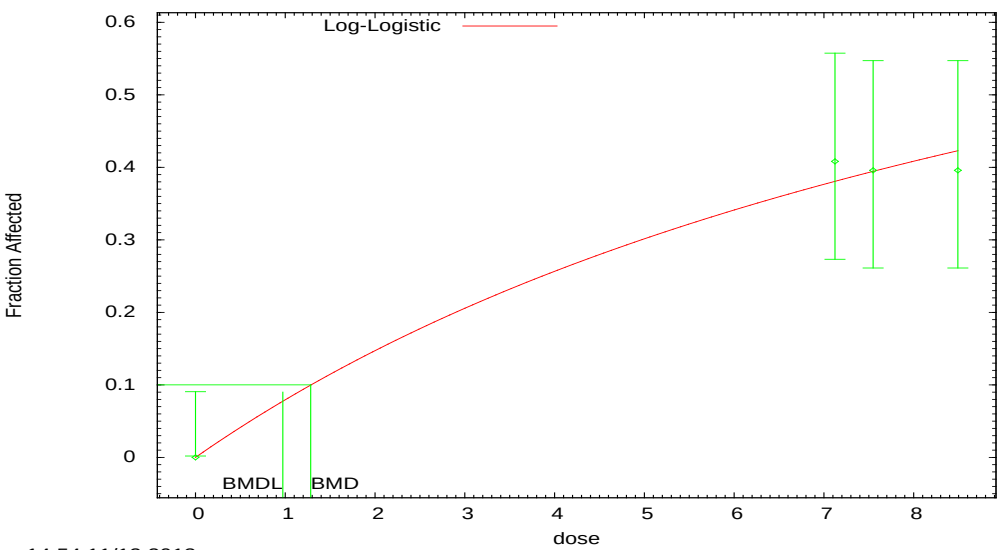
Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:54 11/12 2013

C: LogLogistic_m_red_md4_Lnl-BMR10-Restrict

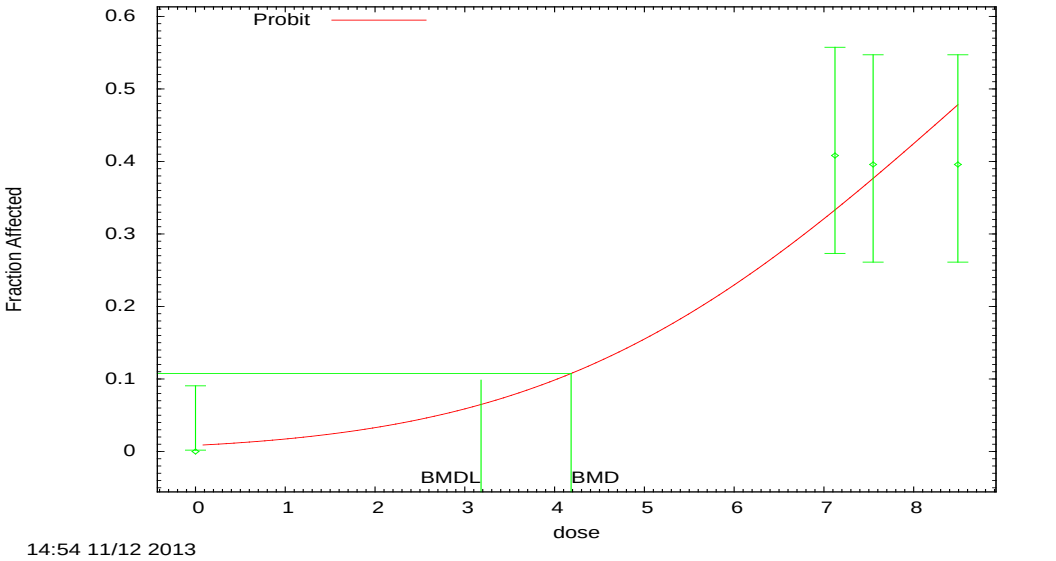
Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



14:54 11/12 2013

D: Probit_m_red_md4_Pro-BMR10

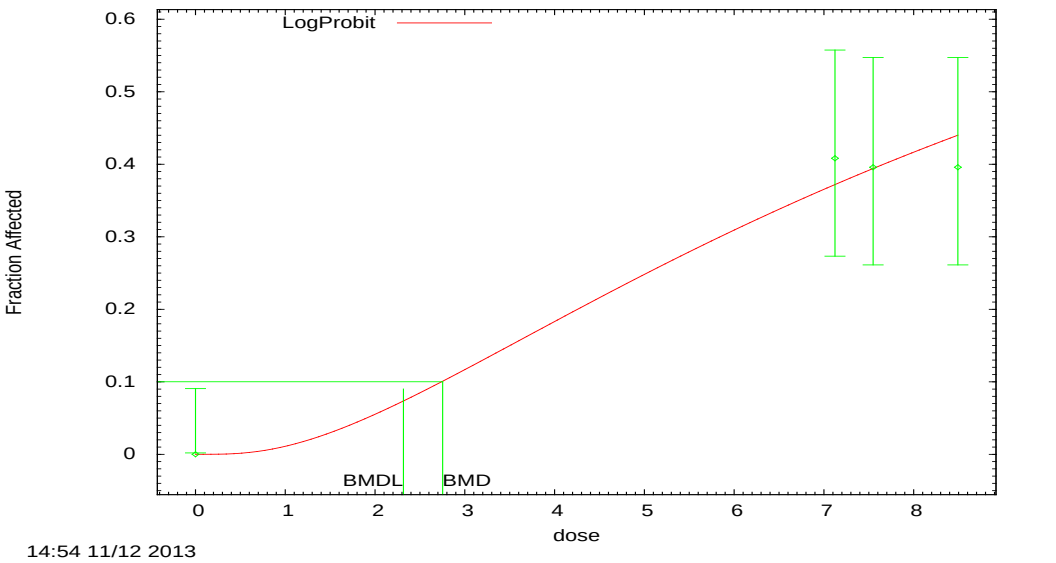
Probit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMI



14:54 11/12 2013

E: LogProbit_m_red_md4_Lnp-BMR10-Restrict

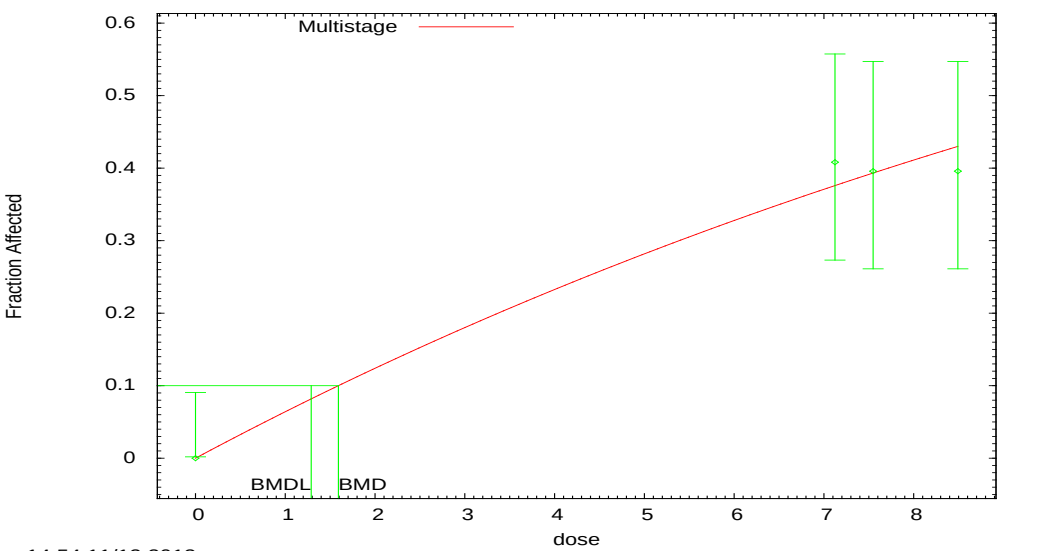
LogProbit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:54 11/12 2013

F: Multistage_m_red_md4_Mst2-BMR10-Restrict

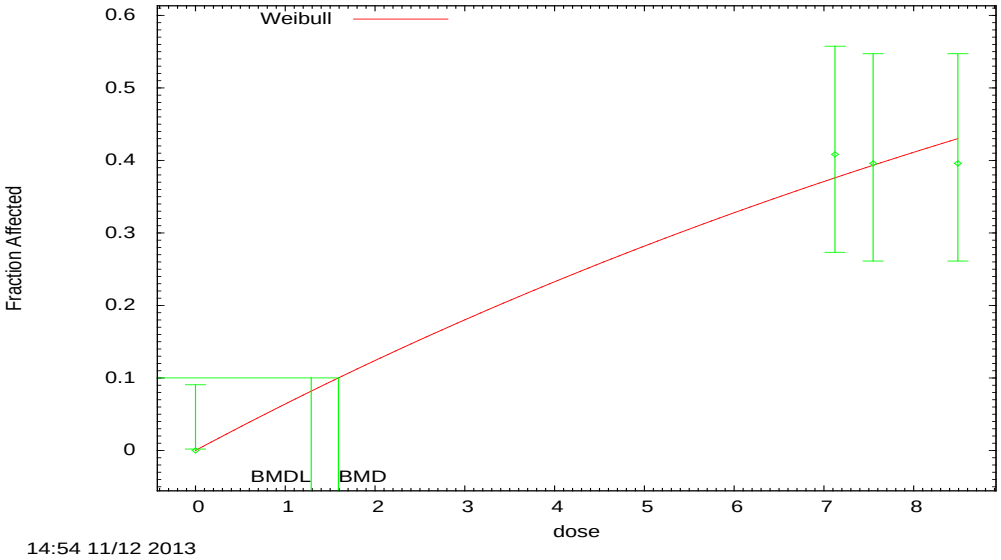
Multistage Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BI



14:54 11/12 2013

G: Weibull_m_red_md4_Wei-BMR10-Restrict

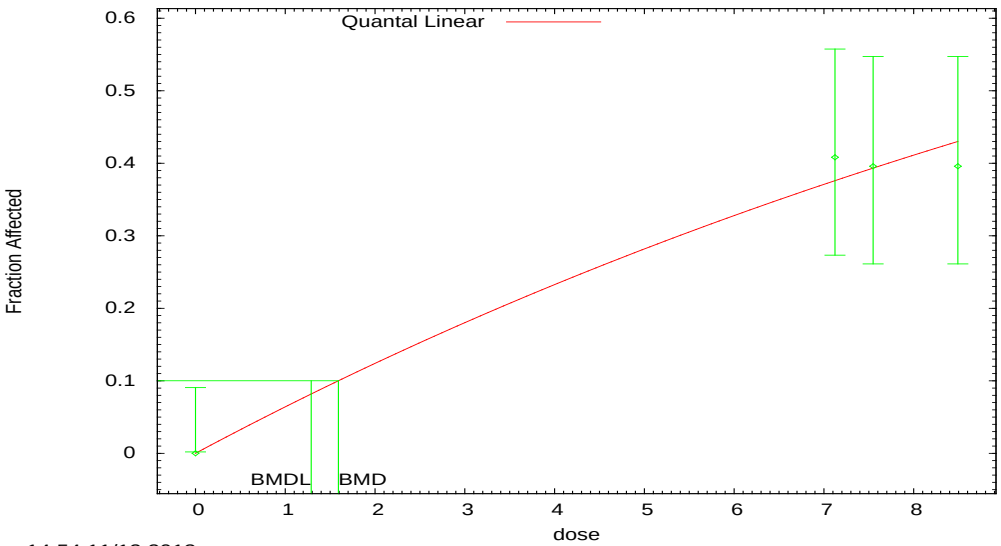
Weibull Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:54 11/12 2013

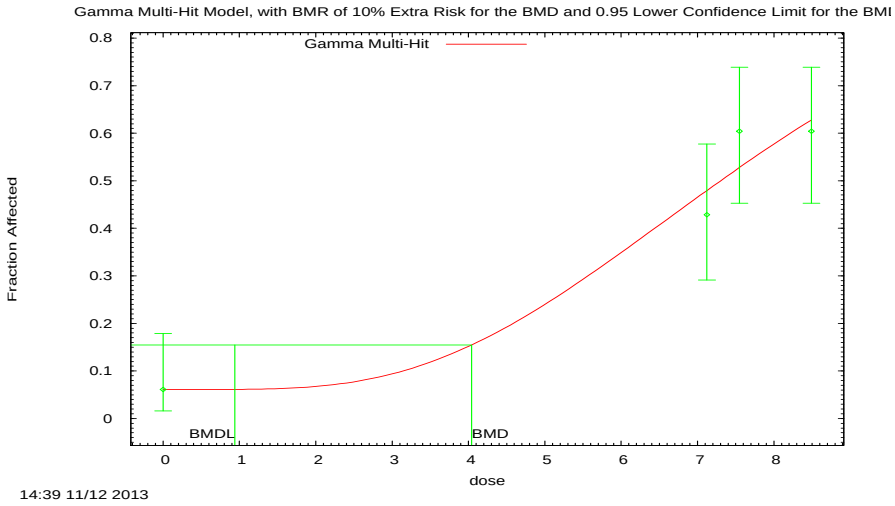
H: Quantal-Linear_m_red_md4_Qln-BMR10

Quantal Linear Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the

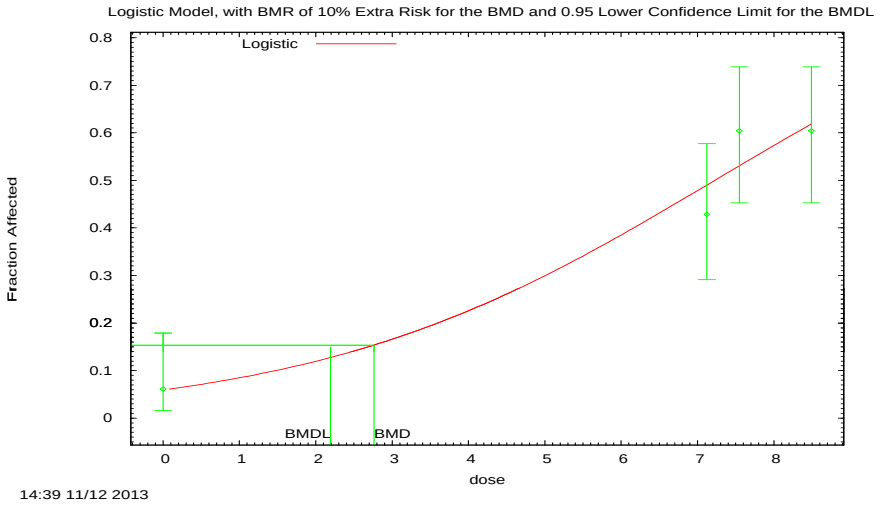


14:54 11/12 2013

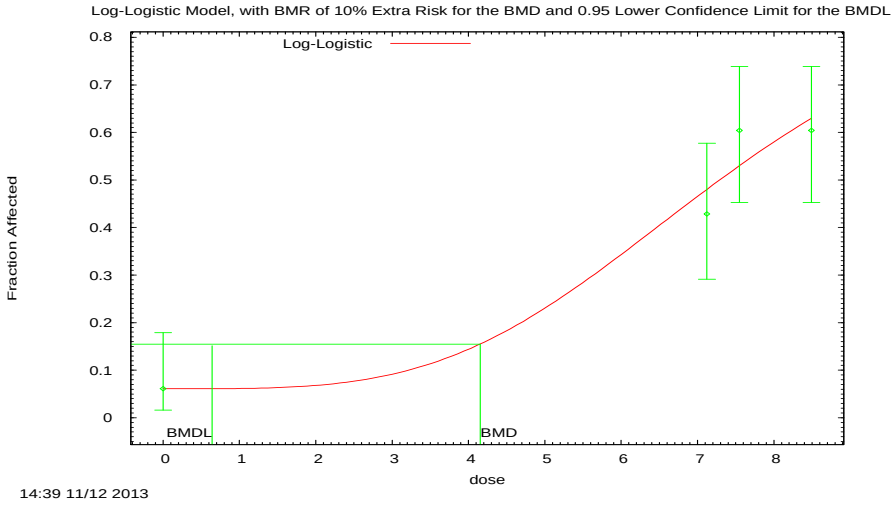
A: Gamma_m_reh_md4_Gam-BMR10-Restrict



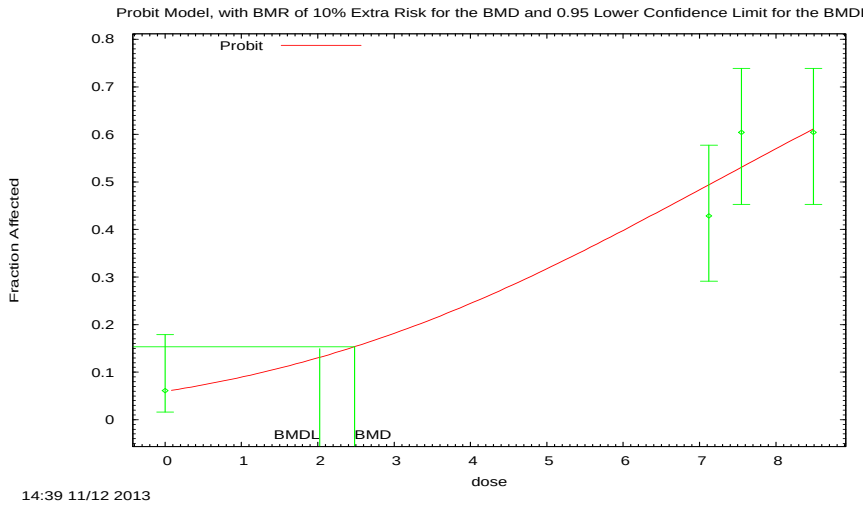
B: Logistic_m_reh_md4_Log-BMR10



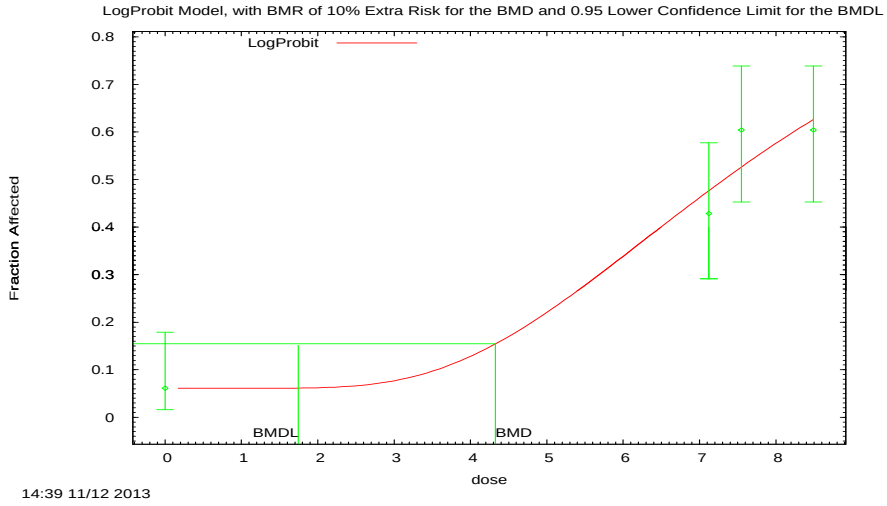
C: LogLogistic_m_reh_md4_Lnl-BMR10-Restrict



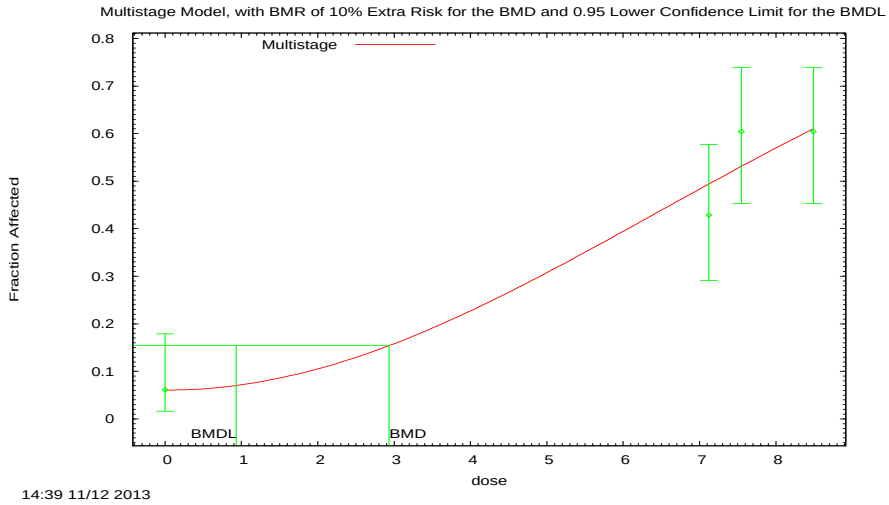
D: Probit_m_reh_md4_Pro-BMR10



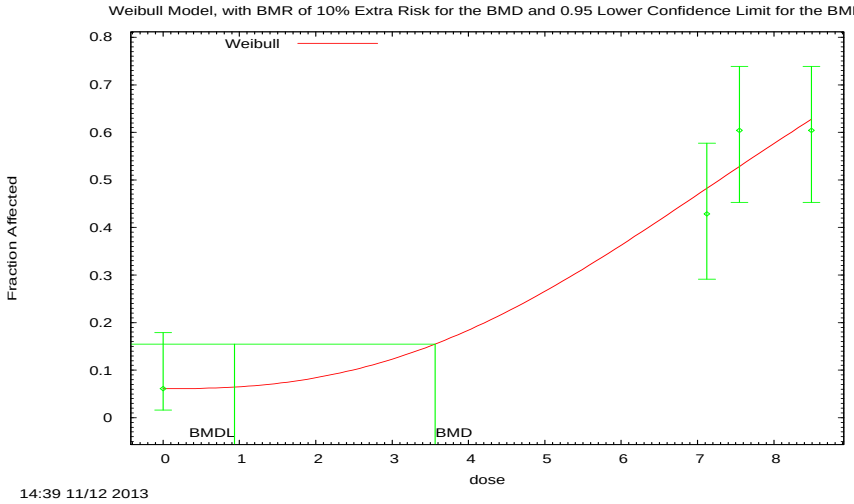
E: LogProbit_m_reh_md4_Lnp-BMR10-Restrict



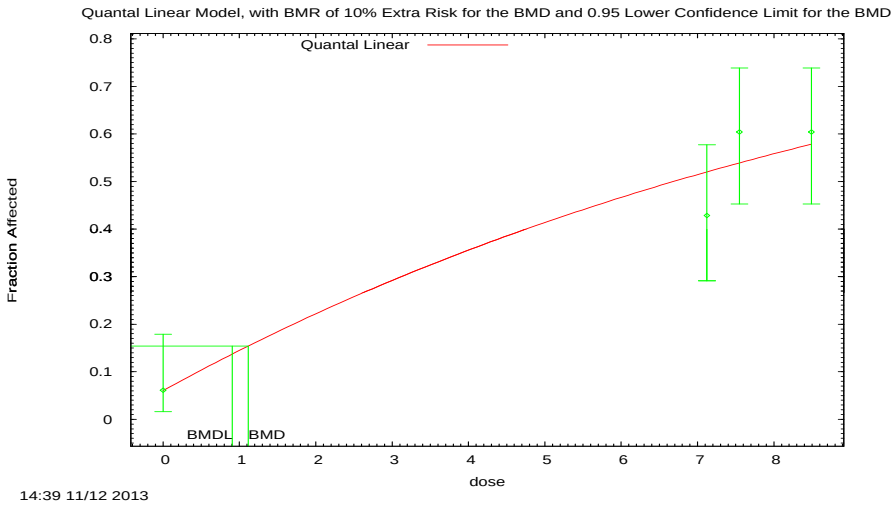
F: Multistage_m_reh_md4_Mst2-BMR10-Restrict



G: Weibull_m_reh_md4_Wei-BMR10-Restrict

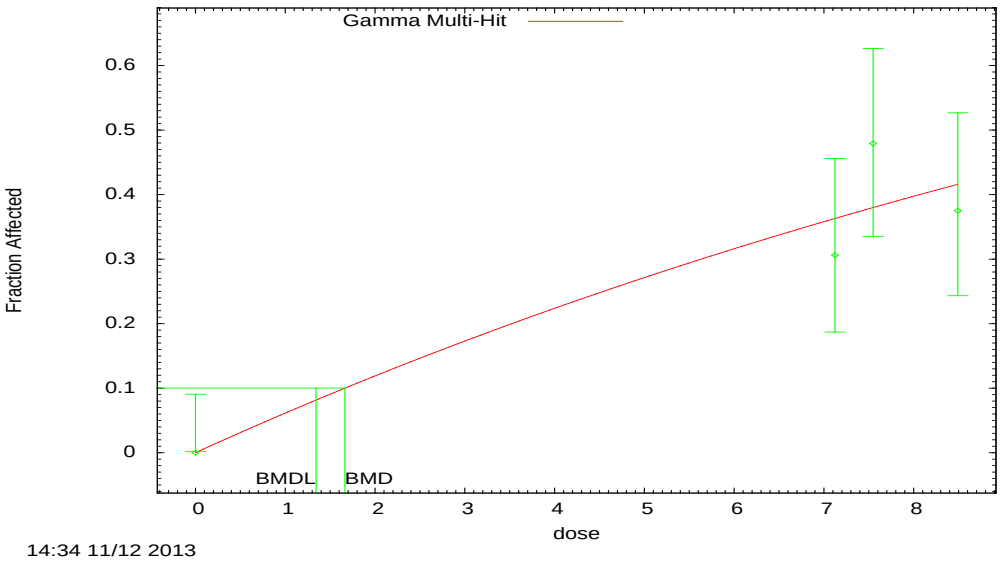


H: Quantal-Linear_m_reh_md4_Qln-BMR10



A: Gamma_m_resm_md4_Gam-BMR10-Restrict

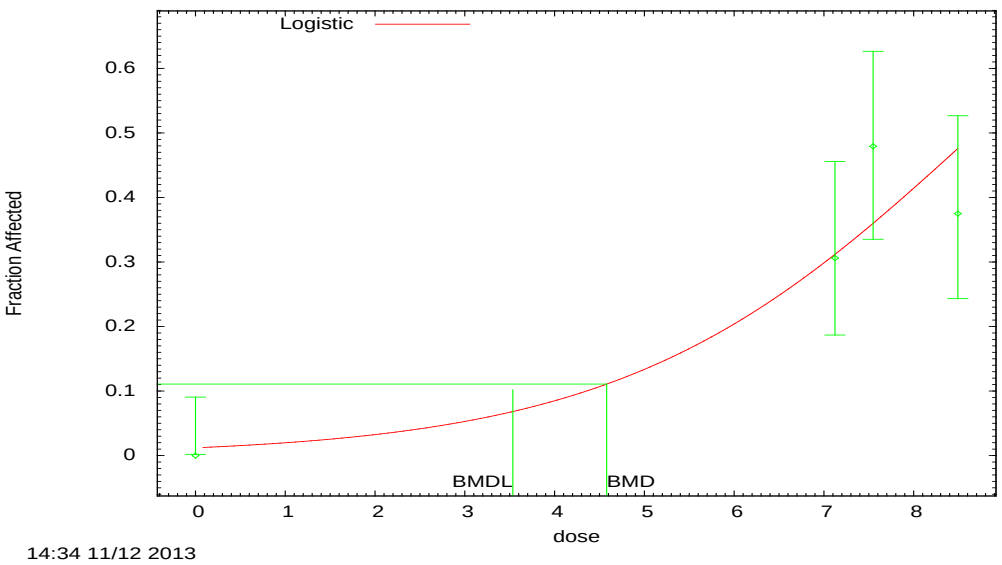
Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



14:34 11/12 2013

B: Logistic_m_resm_md4_Log-BMR10

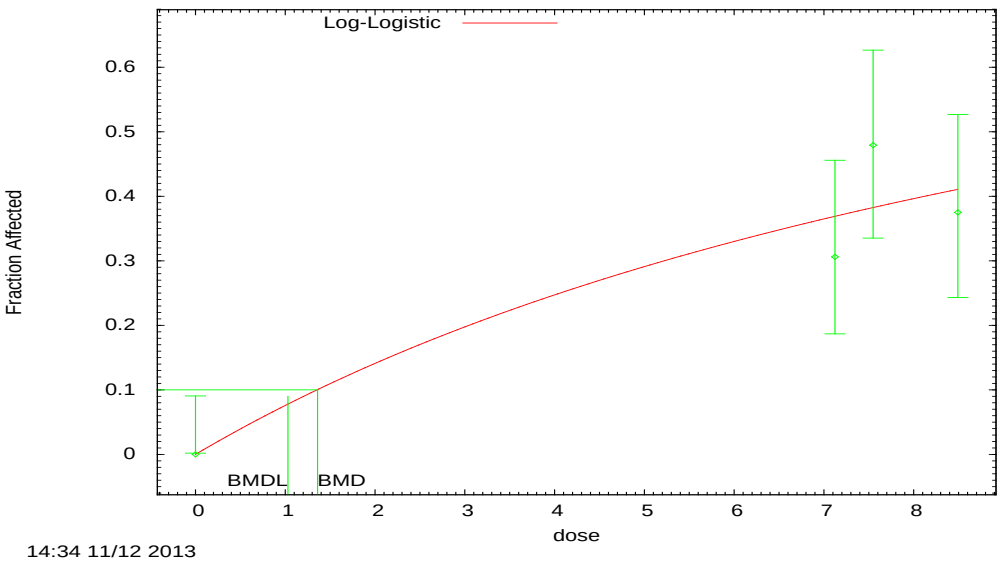
Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



14:34 11/12 2013

C: LogLogistic_m_resm_md4_Lnl-BMR10-Restrict

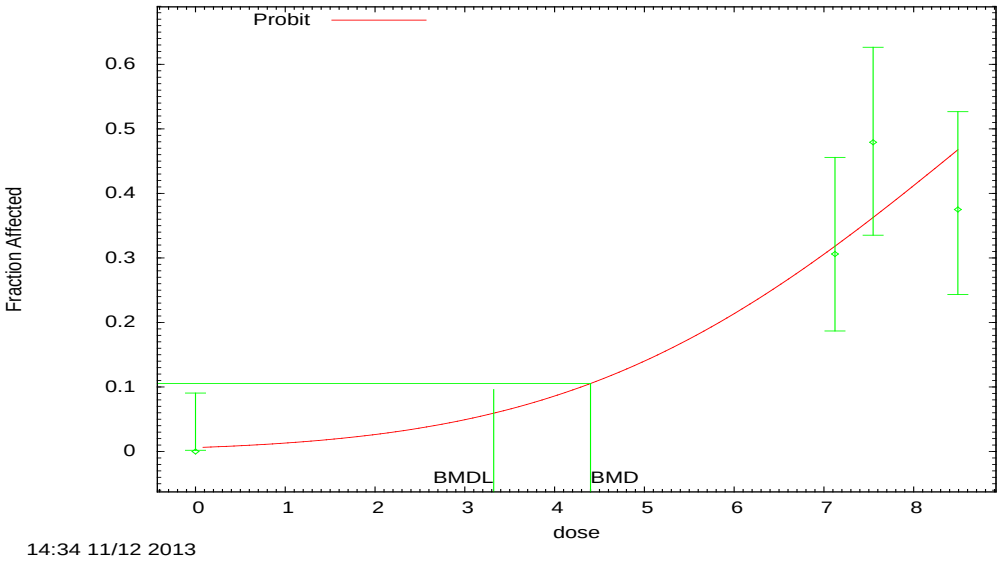
Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



14:34 11/12 2013

D: Probit_m_resm_md4_Pro-BMR10

Probit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMI



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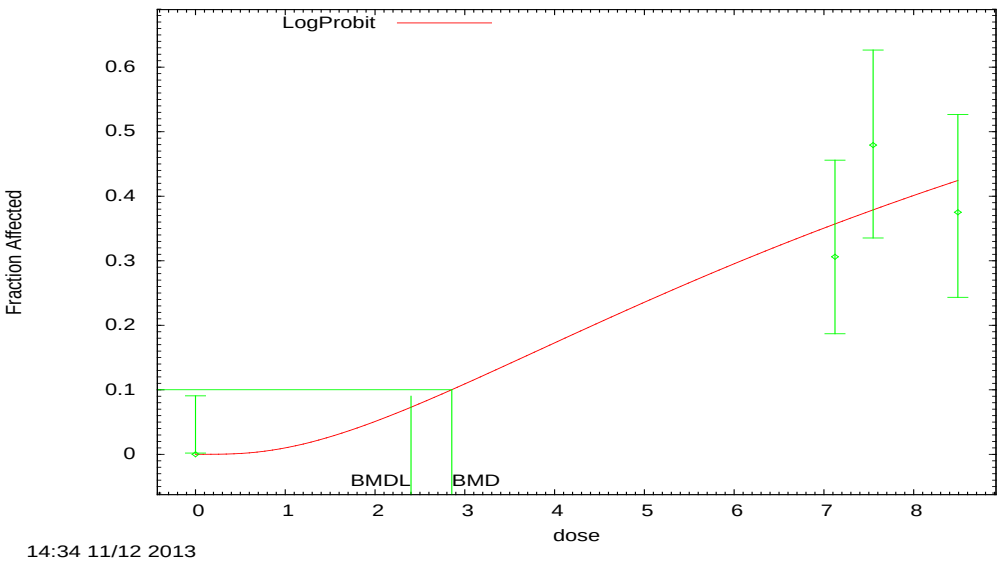
E: LogProbit_m_resm_md4_Lnp-BMR10-Restrict

LogProbit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



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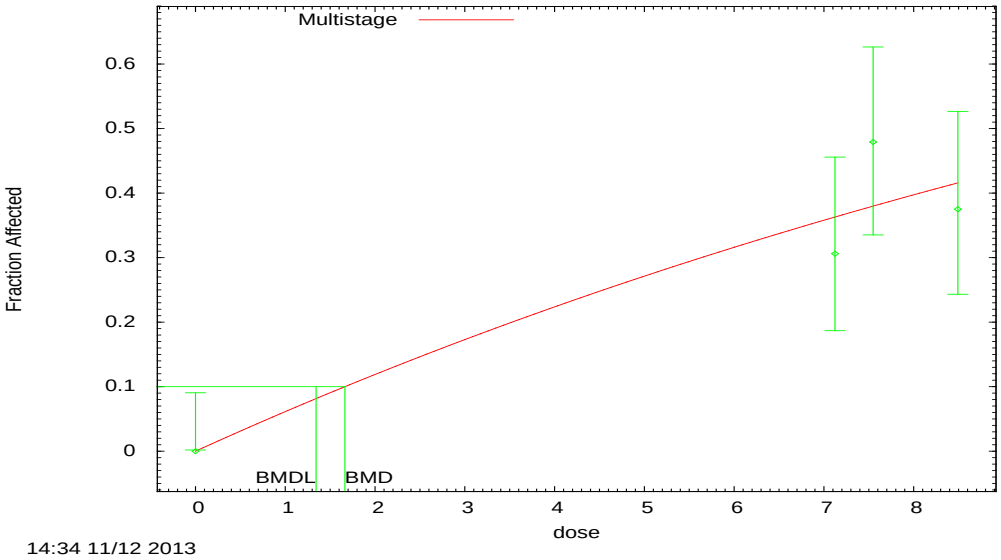
F: Multistage_m_resm_md4_Mst2-BMR10-Restrict

Multistage Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BI



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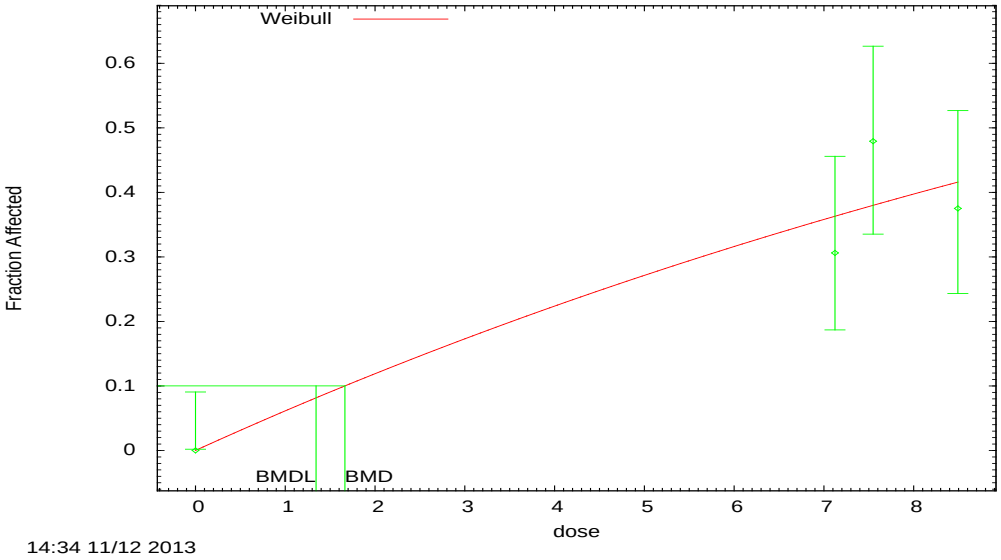
G: Weibull_m_resm_md4_Wei-BMR10-Restrict

Weibull Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BM



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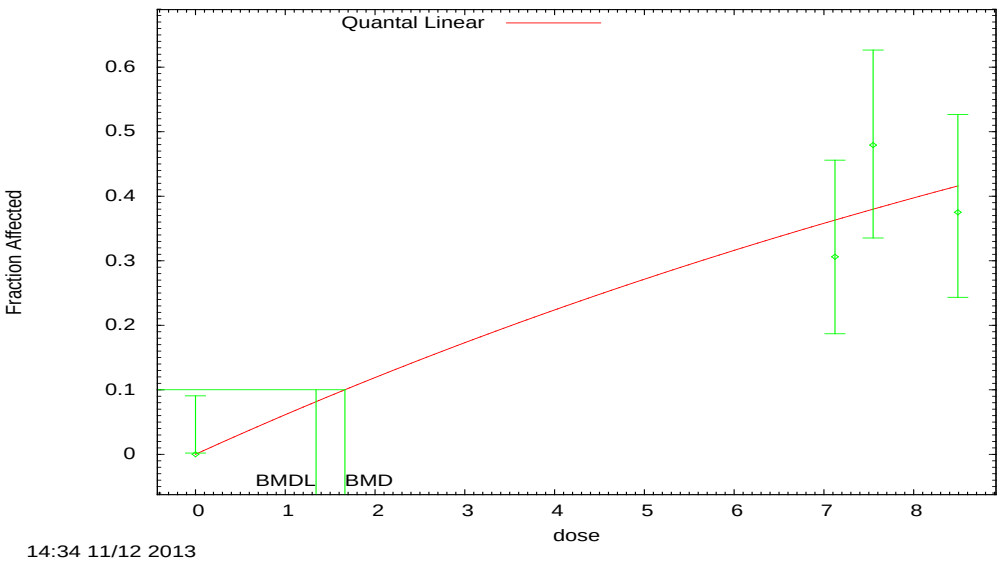
H: Quantal-Linear_m_resm_md4_Qln-BMR10

Quantal Linear Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



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Model Selection Criteria:

Best fit model:

- Select the model with a P-value ≥ 0.1 and with the lowest AIC
  - The lowest AIC model generally had largest P-value, too, but not always.
- If multiple models tie for lowest AIC and largest P-value, select the model with the smallest delta BMD (*i.e.*, BMD - BMDL).

Averaging BMD and BMDL:

Models should be excluded from the average calculation if:

- The model fails to run.
- The model fails to calculate a BMDL or calculates a BMDL of 0.
- The P-value is less than 0.1.
- The AIC is qualitatively larger than other models in the endpoint group.
  - For example, among a set of AIC values containing 2, 3, 4, and 11, the model which produced an AIC of 11 would be excluded from the average calculation.
  - These usually have much lower P-values than the other models, too.

When more than one multistage model fits the data, the multistage model with the lowest AIC should be selected, such that only one multistage model is included in the average calculation.